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review

Impact of a carotid stenosis on cardiac surgery: marker more than risk factor

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SUMMARY: **Impact of a carotid stenosis on cardiac surgery: marker more than risk factor.**

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A concurrent carotid and cardiac disease is the paradigmatic expression of a multidistrictal vasculopathy related to an atherosclerotic burden, that shares the same risk factors and onset pathophysiological mechanisms. The absolute incidence of a stroke after open heart surgery (OHS) is about 2%, higher in case of combined cardiac procedures, with a negative prognostic impact in terms of in-hospital mortality and neurological morbidity. Heterogenous and interlinked risk factors contribute to the genesis of cerebral injuries after OHS outlining patient general features, vascular risk parameters and severity indeces of cardiac disease; a model stroke for patients undergoing cardiac surgery may be helpful so as to identify subsets of patients at high risk and select the most appropriate strategy.

A critical carotid stenosis should be contextualized not as the direct cause of stroke, but as a risk marker of high grade atherosclerotic systemic disease, predicting a potential severe aortic or intracerebral vessel disease and leading to recognize and study carefully these multivascular patients before operation. The idea of carotid plaque as active embolic source is valid only in case of vulnerable plaques in relation to the potential detachment of particulate material. Until now the neurological status, in accordance with symptomatic or asymptomatic carotid stenosis, has markedly influenced the operation timing and the choice of the surgical strategy. Except for special circumstances, we generally suggest a 'reverse staged' surgical strategy with cardiac surgery before carotid timing in elective patients recommending strongly a pharmacological neuroprotection relied on the administration of Sodium Thiopentone. Most of carotid stenosis in patients undergoing OHS is asymptomatic and doesn't represent a proven independent risk factor for postoperative stroke; indeed, we advocate that synchronous surgical treatment of both carotid and cardiac lesions is burdened from higher perioperative mortality and stroke rates rightfully unjustifiable according to potential benefits.

KEY WORDS: Carotid stenosis - Stroke - Open heart surgery - Neuroprotection.

Introduction

A concurrent carotid and cardiac disease is the paradigmatic expression of a multidistrictal vasculopathy related to an atherosclerotic burden, that shares the same risk factors and onset pathophysiological mechanisms. The absolute incidence of a stroke after open heart surgery (OHS) is about 2%, higher in case of combined cardiac procedures, with a negative clinical prognostic impact in terms of in-hospital mortality rate and neurological morbidity. Epidemiological data underline the common finding of a hemodynamically significant carotid artery stenosis (CAS) in patients, mostly asymptomatic, undergoing cardiac surgery with an incidence ranging from 1.7% to 12% and an average of 8% in case of CABG; on the other side, approximately one third of patients with a carotid stenosis to treat surgically is affected by a synchronous critical coronary artery disease (CAD).

Over the last decades, multiple surgical strategies have been proposed, through both synchronous and staged modalities, nevertheless without achieving predominant guidelines because of lacking randomized clinical trials and bias influence; thus, until now the neurological status, according to symptomatic or asymptomatic carotid lesions, has markedly influenced

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the operation timing and the choice of the surgical strategy.

But is really the carotid stenosis such an important risk factor for perioperative stroke that deserves a surgical treatment? And the benefits of a carotid revascularization, whatever the timing may be, could justify the periprocedural risks, too serious, described in the systematic reviews? Indeed, when we deal with this complex clinical controversy, *Quid agam*?

Hereafter we will focus on the effective role of critical carotid stenosis about the pathophysiology of neurological disorders after cardiac surgery, simultaneously analyzing surgical, anesthetic and perfusionist strategies in the attempt to ensure the best possible neuroprotection model and avoid worse neurological outcomes.

Clinical background and applications

Pathogenesis of a postoperative cerebral attack is usually ischemic with an embolic and/or hypoperfusive mechanism, whereas a primary cerebral hemorrhage seldom occurs complicating on the contrary more frequently a primitive ischemic stroke.

The first 24 hours after cardiac surgery represent the most critical time span, in which happen more than half of cerebral injuries, that are expression of damage intraoperative or just after anesthesia recovery, with higher lethality.

Cerebral embolic sources arise from particulate material of a severe atherosclerotic aortic disease, especially in case of parietal thickness > 5 mm or mobile atheroma, or from a perioperative atrial fibrillation, often paroxysmal; also air emboli, frequently after unsatisfactory debubbling process, may generate neurocognitive impairments or other neurological postoperative complications.

Cerebral hypoperfusion can follow a perioperative arterial hypotension, as in case of low cardiac output or vasoplegic episodes, with cerebral perfusion pressures inadequate to substain brain vasal autoregulation which may be already exausted; effects of hypoperfusion lead to penumbra area ischemia or delayed washout of embolic load.

A model stroke for patients undergoing cardiac surgery (19) may be helpful so as to identify subsets of patients at high risk and select the most appropriate strategy; in a correct diagnostic algorythm a start physical investigation is advisable, checking the presence of audible neck bruits and addressing selected patients to ultrasonographic study (34).

Heterogenous and interlinked risk factors promote after OHS the genesis of cerebral injuries (15), including main patient general features, vascular risk parameters and severity indeces of cardiac disease (1) (Table 1).

A serious aortic atherosclerotic disease, following Katz classification, is a strong predictive element of an important intracranic atherosclerosis, as well as the frequency of peripheral artery disease (PAD) is prevalent in patients who had stroke; in CABG patients, Gensini score > 50.5 and high Syntax score II may predict a significant carotid stenosis (30), identifying patients at very high cardiovascular risk. The idea of an unique polivascular disease must be prevalent, dealing with CAS, CAD e PAD not as single epiphenomena, but as different features of the same pathology.

Firstly, the relationship between a postoperative stroke and a carotid stenosis relied on diminished flow and impaired autoregulation distally to the narrow tract; already in 2002 Naylor et al. (11) suggested that about 60% strokes weren't linked to carotid stenosis and in 2011 a meta-analysis and systematic review reported by the same Naylor and Brown introduced the concept of carotid lesion as a marker more than as a cause of stroke.

TABLE 1 - RISK FACTORS FOR NEUROLOGICAL COMPLICATIONS AFTER CARDIAC SURGERY.

Markers of general patient risk
Age at surgery
Female sex
Diabetes mellitus
Smoking
End stage kidney disease/Dialysis
Markers of vascular risk
Peripheral vascular disease
Previous TIA or stroke
Carotid stenosis
Aorta atherosclerotic disease
Subcortical small vessel disease
Markers of severity of cardiac disease
Poor left ventricular function
Pulmonary hypertension
Critical preoperative state (IABP – pharmacological and ventilatory support)
Acute coronary syndromes

Thereby, critical carotid stenosis must be seen not as the direct cause of stroke (12), but as a risk marker (14, 15) of high grade atherosclerotic systemic disease predicting a potential severe aortic arch or intracerebral vessels disease, allowing to recognize and study carefully these multivascular patients before surgery.

A carotid plaque represents an active source of embolism only in case of vulnerable or ulcerated plaques; the morphology combined with the plaque composition is more important than stenosis grading for the risk stratification because of dynamic changes associated to adverse neurological outcomes.

The embolic risk is really higher in case of soft and ulcerated carotid plaques (13) (Figure 1 A, B, C, D) even in case of asymptomatic patients, in relation to potential detachment of particulate material with migration towards the intracranial circulation as a result of turbulent flows around friable plaque.

In a wide review, lateralization and distribution of postoperative stroke have clarified that the relationship between carotid stenosis and stroke is not really significant (33).

Few strokes are in the large vessel category in conformity with TOAST criteria, such as Libman et al. (21) also reported an incidence of 16% for lacunar syndromes secondary to intracranial atherosclerosis. Barbut et al. (20) postulated that brain injuries are mostly bilateral, multiple or in the vertebro-basilar district, suggesting an unexact association between carotid stenosis and the involved ipsilateral cerebral emisphere and ascribing embolic sources to aortic plaques or an intracardiac thrombus; in their work only few patients had a hemodynamic failure that could justify the most important mechanism of stroke.

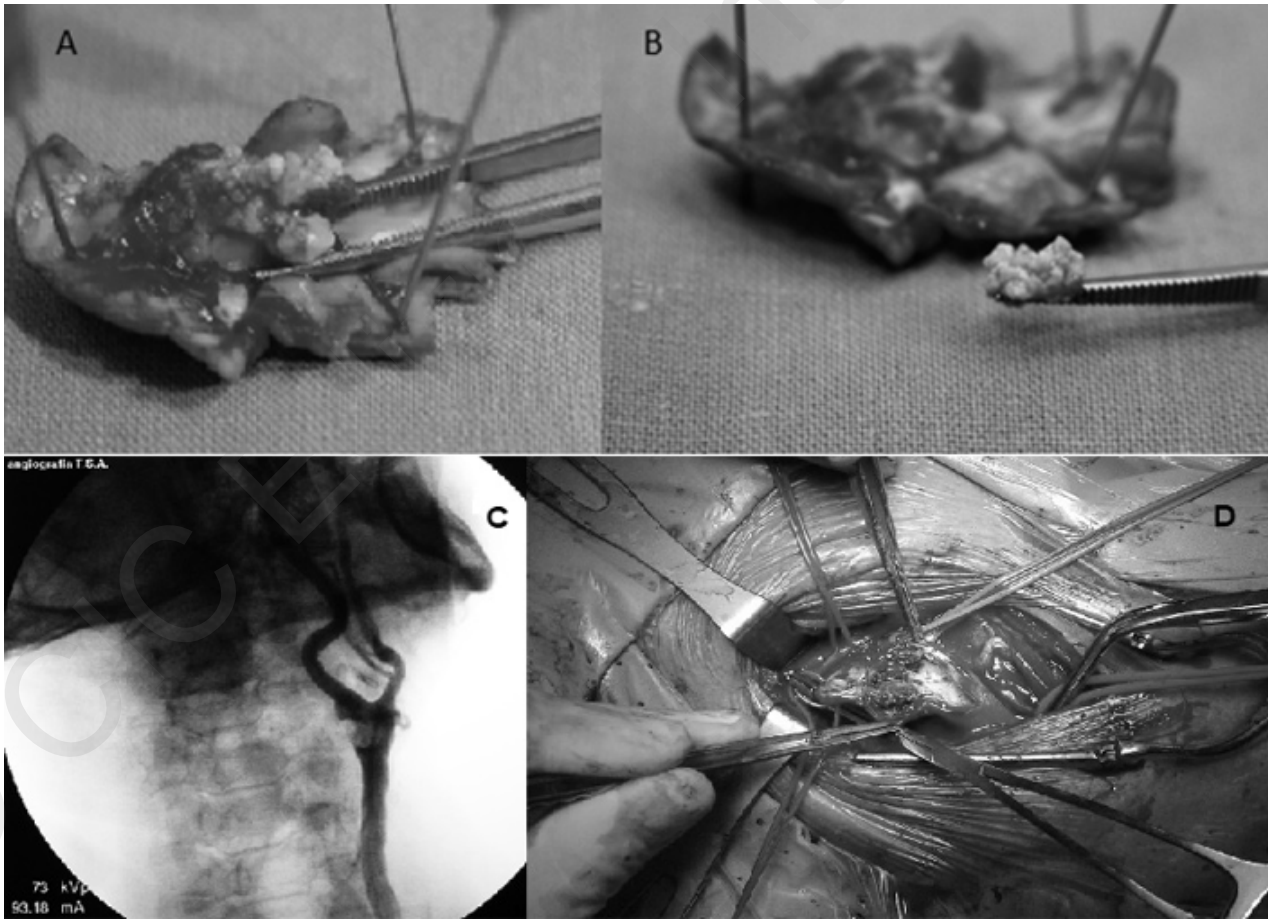

Figure 1 - A-D Intraoperative photos show the presence of irregularities and cavities within a 'soft' carotid plaque (A) and the facility into detaching embolic material from surface plaque by using forceps (B). Angiographic imaging illustrates an ulcerated carotid niche, seen as a crater from the lumen in a stenotic plaque with plus image in profile drawn by contrast entering (C), whereas an intraoperative view shows ledges into the lumen arising from fragmented plaque ulcerations with microthrombi formation (D).

Moreover, Wikyt et al. (35) documented multiple infarcts in bilateral hemispheres, supporting the thesis that several perioperative strokes affect cerebral areas outside of a single carotid artery.

ON-Pump and OFF-Pump surgery: pros and cons

Nowadays prolonged cardiopulmonary bypass (CBP) times are well-known predictors of adverse neurological outcome; the loss of pulsatile flow on-pump may entail worse perfusion indexes in patients with microcirculation and cerebral vascular autoregulation sometimes basically altered, especially in elderly population.

Despite the use of α-stat ph management, during CPB brain circulatory reserve may be subject to a further impairment (6-10); cerebral flow is directly proportional to perfusion pressures, that may be influenced by hematocrit values on pump beyond the grading and length of carotid stenosis. On the basis of leading role played from perfusion pressures, mean arterial pressure (MAP) values must be mantained above 70 mmHg, administrating vasopressors too, because pump flows don't influence the mantainance of an adequate cerebral autoregulation.

MAPs values out of the subjective autoregulatory range of each patient promote neuronal tissue damages, especially in case of compromised or incomplete Willis circle connections; a MAP value already < 10 mmHg from the baseline is just considered by some Authors as a worse predictor of neurocognitive disturbances or bilateral strokes linked with high in-hospital mortality.

The role of a low hematocrit during CPB as an independent risk factor for postoperative stroke has already been studied by Karkouti et al. (9); anemic status, due to excessive hemodiluition or surgical bleeding, must be checked and corrected, if necessary, through transfusions in order to gain values Hgb ≥ 7.5 or Hct ≥ 22%, as recommended by Habib et al. (8).

In the perioperative time a severe hyperglycemia is often observable, so that a tight glycemic control (<140 mg/dl) is advisable not to reinforce a cerebral damage, as well as hyperhermia during re-warming from mild hypothermia managed on-pump may be harmful.

Embolic risks of aorta manipulation during cannulation/decannulation and clamping/declamping procedures can be overcome by a beating heart surgery, abolishing the relay of atherothrombotic debris from a diseased aorta; in CABG patients the creation of proximal anastomoses through venous grafts directly on the mammary arteries could help not to mobilize further plaques from an atherosclerotic aorta.

Furthermore, use of OFF-Pump surgery allows to avoid a systemic inflammatory response syndrome with fibrinolytic shutdown and hypoperfusion related to CPB that can exacerbate brain injuries, whatever genesis may have been, in association to ischemia/reperfusion damages.

Pharmacological neuroprotection

Pharmacological strategies usually aim at protecting brain during surgery improving the tolerance to injuries with a rationale that mainly implies the reduction of cerebral energetic metabolism.

Among pharmacological agents we strongly advocate the use of Sodium Penthotal (26), an ultrashort acting barbiturate in comparison with other drugs of the same cathegory (as Luminale), suppressing neurotransmission through a GABA receptor-mediated mechanism.

Thiopental, already used as additive neuroprotector during deep hypothermic circulatory arrest, reduces brain oxygen consumption and cerebrovascular resistances improving cerebral circulation and cerebral oxigen delivery during CBP; the administration of this barbiturate is performed by a single intraoperative bolus dose in the central phase at clamped aorta, mitigating clinical expression of possible embolisms or reducing cerebral infarcts size.

Other neuroprotective drugs are low-affinity NMDA receptor antagonists blocking sodium channels and Aprotinin which acts by a mechanism related to antinflammatory and antifibrinolytic features; innovative therapies have been recently proposed by administrating Pexelizumab, a monoclonal antibody against C5 fragment of complement system.

Neuromonitoring techniques

Near-infrared spectroscopy (NIRS) is a very useful non-invasive methodic monitoring continuously re-

al-time regional cerebral tissue oxigen saturation (rSO_2) (25-27) with the aim of assessing functional and circulatory reserve in the phases of deep sedation.

Brain metabolic status reflects arterial and venous hemoglobinic saturation and the cerebral oxigen supply-demand balance is expressed so that:

- rSO_2 < 10% from baseline values underline a desaturation with cerebral dysfunction
- rSO_2 < 20% from baseline values denote a critical desaturation and a bad cerebral perfusion.

Demand-delivery mismatch can depend on hemodynamic failure, outlining that a correct cerebral oxigenation needs an adequate cardiac output and oxigen content in cardiac surgery patients with CAS more than surgical cohorts without CAS (27).

A basal asimmetry of baseline rSO_2 values is sometimes observable in relation to a mechanical, positional cause; simply adjusting head position, *ab estrinseco* compression from atlante on the diseased carotid artery is abolished, therefore improving perfusion of ipsilateral cerebral hemisphere.

Main benefit of intraoperative cerebral oximetry consists in detecting early cerebral malperfusion allowing to adopte all suitable corrective measures (25).

Corrective steps making better oxigen delivery aim at increasing:

- pump flows to raise cardiac index > 2.0 L/min/m^2
- MAP (70-90 mmHg) by optimizing perfusion pressures
- pCO_2, a strong autocoid cerebral vasodilatator decreasing gas-inflow during CPB or sweeping, reaching a mild hypercapnia too (40-45 mmol/L)
- hematocrit values.

On the other hand, some arrangements reduce cerebral metabolism and decrease oxigen demand by:

- deeping anesthesia, increasing FiO_2 in order to obtain higher arterial pO_2
- decreasing body temperature (mild hypothermia).

Cerebral blood flow autoregulation may be monitored through a NIRS-based system calculating a cerebral oximetry index (COx) (16), a Pearson's dynamic correlation coefficient gained in relation to rSO_2 and MAP values; a COx > 0.3 during CPB underlines an impaired, dysfunctional cerebral autoregulation and higher risk of potential adverse neurological outcome (36).

As alternative option to NIRS, transcranial doppler (TCD) (24) reflects properly cerebrovascular hemodynamic changes and identifies patients with CAS that have a CBF autoregulation already exausted before CPB (10), evaluating the mean flow velocity of middle cerebral arteries (MCA).

The loss pulsatile flow due to CPB beginning and the fall of peripheral resistances lead to a MAP reduction; secondary reactive cerebral vasodilatation in arterioles distally to MCA increases blood flow velocity. Moreover, TCD is very sensible to detect cerebral embolic signals that can occur without NIRS signal changes in non-monitored sites.

Caveats

The origins of dilemma about the optimal surgical strategy of a concurrent carotid and cardiac disease lie in the supposed higher risk of MI treating firstly a carotid stenosis (*staged* modality*)*, or of stroke when cardiac surgery is the first surgical step (*reverse staged* modality).

Following last ACC/AHA and ESC/EACTS guidelines (22, 23, 28), a carotid revascularization in cardiac surgery patient may be reasonable in symptomatic unilateral carotid stenosis or bilateral (even if asymptomatic) lesions and in case of unilateral severe stenosis associated to a contralateral carotid occlusion (Class IIb).

The timing of revascularization, synchronous if under the same anesthesia or staged, is related to the severity and instability of each myocardial and neurological dysfunction (Class IIa); the choice of carotid revascularization option (CEA or stenting) should analyze comorbidities, carotid anatomy and urgency level (Class IIa), underlining that a dual antiplatelet therapy must be carried out at least one month before the cardiac procedure in patients who underwent a carotid stenting (Class I).

Asymptomatic lesions are not a proven independent risk factor for postoperative stroke (4, 33, 38), as postuled also from CABACS trial, that, despite early interrupted, suggests no intervention on an asymptomatic carotid stenosis (2, 3, 38); indeed, about 95% of carotid stenosis in cardiac surgery is asymptomatic, reinforcing the idea of a *'reverse staged'* strategy.

Urgency and emergency, as unstable angina or involvement of left main coronary artery/equivalent LAD proximal subocclusion, require reasonably a first cardiac time; then, we strongly believe that synchronous surgical treatment of both carotid and cardiac

lesions is burdened by higher perioperative mortality and stroke rates rightfully unjustifiable according to potential benefits (7, 17, 31).

A first carotid time is evaluable in valvular patients or stable angina only in case of bilateral symptomatic carotid stenosis (approximately only 1.5% of patients undergoing OHS) or unilateral one with contralateral occlusion because of high risk of adverse neurological outcomes in these subgroups of patients.

In CABG patients hybrid coronaric procedures, through minimal surgery without cardiac lussations as LIMA-LAD ± SVG-RCA Off-pump followed by PCI, preserve heart from dangerous displacements in attempt to carry out distal anastomoses on posterolateral cardiac surfaces, anyway avoiding CPB-related disadvantages. It is essential to remember that a hemodynamic stability during and after surgery prevents the negative impact of a diffuse atherosclerosis.

In presence of unilateral symptomatic carotid stenosis, a recent stroke needs at least one month before cardiac surgery in elective patients, in order to restore autoregulatory mechanisms and repair parenchimal damages, decreasing the risk of conversion into emorrhagic area and allowing the evaluation of recurrence risk and cerebral lesion size. The magnitude and severity of neurological dysfunction should turn us to choose rationally the strategy *case to case*, not excluding at first glance a *"reverse-staged"* approach, by adopting all corrective arrangements.

Carotid angioplasty stenting: a good staged ibrid approach?

Sapphire trial results have shown safety and efficacy of carotid stenting (CS) in comparison with CEA, thus current trends suggest CS before OHS as an attractive and alternative less invasive option (18, 29, 32, 37) associated to lower events rates.

Naylor et al. (40) have performed a review and metanalysis documenting comparable outcomes for both staged CS-CABG and CEA-CABG (36); in addition, some centers propose a CS followed by OHS after few hours (39).

Nevertheless, "one-day" surgical strategy is strongly limited by:

- a required aggressive antiplatelet regimen with higher postoperative bleedings, as suggested from non-randomized SHARP study (5)
- an acute nephropathy due to contrast use
- a cerebral hyperperfusion syndrome related to just alterated autoregulation mechanisms.

In case of CS periprocedural hemodynamic changes, via baroreceptorial stimulations, may be very dangerous in patients affected from severe aortic stenosis or very crucial coronaropathy; indeed, in stable patients the compromise proposed by Van der Heyden et al. (14) seems acceptable, focusing on a delaying time of 2-3 weeks between CS and cardiac surgery to administrate a double antiplatelet therapy against a carotid restenosis up to 5 days before the cardiac surgery day, whereas no discontinuation would be performed in case of urgency/emergency.

Conclusion

The management of a cardiac surgery patient with relevant synchronous carotid stenosis represents a compelling challenge, in which interlinked advancements of surgical, anesthetic and perfusionist techniques could help to overcome the difficulties of a multidistrictal vascular patient.

The risk stratification for postoperative strokes always starts with the preoperative identification of patients at high risk. Except for special circumstances, such as symptomatic bilateral carotid stenosis or ICA occlusion together to contralateral hemodinamic stenosis, we generally suggest a *reverse staged* modality as surgical strategy in elective patients advocating a pharmacological neuroprotection based upon the use of sodium thiopentone.

Beyond a specific reference to ulcerated or soft carotid plaques because of their poor prognosis, anyway we look more and more at the role of carotid stenosis as a risk marker of generalized atherosclerosis rather than as a risk factor for strokes after cardiac surgery.

Conflict of interest

The Authors declare no conflict of interest relevant to this publication.

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