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Μεταπτυχιακή Διπλωματική Εργασία

"RISK STRATIFICATION FOR STROKE IN PATIENTS UNDERGOING CABG"

υπό

ΑΛΕΞΑΝΔΡΑΣ Α. ΛΙΑΚΟΠΟΥΛΟΥ

Επικουρικής Επιμελήτριας Β' Καρδιοχειρουργικής

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διακρατικού Μεταπτυχιακού Διπλώματος Ειδίκευσης

«Υπερηχογραφική Λειτουργική Απεικόνιση για την πρόληψη & διάγνωση των αγγειακών παθήσεων»

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ΕΥΧΑΡΙΣΤΙΕΣ

Αισθάνομαι την ανάγκη να ευχαριστήσω θερμά:

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Αλεξάνδρα Α. Λιακοπούλου

ΠΕΡΙΛΗΨΗ

Η γήρανση του πληθυσμού συνδέεται με αύξηση του επιπολασμού της στεφανιαίας νόσου. Αυτή η επιδημιολογία οδηγεί σε αύξηση των ασθενών που τελικά θα υποβληθούν σε χειρουργική επαναγγείωση (αορτοστεφανιαία παράκαμψη-CABG), μια επέμβαση που τους εκθέτει σε αυξημένο κίνδυνο εγκεφαλικού επεισοδίου περι-εγχειρητικά. Η καταστροφική ακολουθία εγκεφαλικού επεισοδίου και CABG δημιουργεί μια σημαντική ιατρική κατάσταση, που συνδέεται με σοβαρό κίνδυνο νοσηρότητας και θνησιμότητας. Η κύρια πηγή των εμβολικών συμβαμάτων είναι οι καρωτίδες και η αριστερή κοιλία. Η προ-εγχειρητική ταυτοποίηση των πιο ευάλωτων ασθενών πρέπει να είναι διεξοδική.

Ο κύριος στόχος θα πρέπει να είναι η ταυτοποίηση του κλινικού ιστορικού των ασθενών, καθώς αρκετές μεταβλητές όπως το ιστορικό πολλαπλών εγκεφαλικών επεισοδίων, η καρωτιδική νόσος, η καρδιακή ανεπάρκεια κ.λ.π. είναι ισχυροί παράγοντες πρόκλησης εμβολικών επεισοδίων στο κεντρικό νευρικό σύστημα, ενώ διάφορες απεικονιστικές μέθοδοι (συμβατική ή υπολογισμένη αγγειογραφία, υπέρηχος) παρέχουν επικουρικές πληροφορίες. Ως εκ τούτου, η διαστρωμάτωση του κινδύνου για εγκεφαλικό επεισόδιο στην εποχή της χειρουργικής επέμβασης είναι σημαντική. Έχουν αξιολογηθεί διάφορα εργαλεία, χωρίς όμως να είναι ικανά να προβλέψουν με ακρίβεια τον ασθενή υψηλού κινδύνου. Από την άλλη πλευρά, η ορθολογική διαχείριση των αντιθρομβωτικών παραγόντων και των στατινών μπορεί να μειώσει τον περι-εγχειρητικό κίνδυνο.

Λέξεις-κλειδιά: ισχαιμικό εγκεφαλικό επεισόδιο, CABG, στεφανιαία νόσος, καρωτιδική στένωση, υπερηχογράφημα doppler, θρομβοεμβολή

ABSTRACT

The ageing of the population is associated with an excessive accumulation of coronary artery disease. This epidemiology entity leads to increase of the patients who will eventually undergo surgical revascularization, an operation that expose them to advanced risk of peri-operative stroke. This ruinous sequence of stroke and CABG creates a significant medical state, associated with a grievous morbidity and mortality risk. The main source of the embolic events is the carotid arteries and the left ventricular. The pre-operative identification of the more vulnerable patients must be thorough. Principle goal is to encapsulate the clinical history of the patients, since several variables such as previous history of stroke, carotid artery disease, heart failure, etc. are strong inducers of embolic events in the central nervous system, whereas several imaging modalities (conventional or computed angiography, duplex ultrasound) provide adjuvant information. Therefore, the risk stratification for stroke in the surgery era is of importance. Several tools have been evaluated, without being capable of predict with accuracy the high-risk patient. On the other hand, rational management of antithrombotic agents and of statins may diminish the peri-operative risk.

Key words: ischemic stroke, CABG, coronary artery disease, carotid stenosis, Doppler ultrasound, thromboembolism

Chapter 1. EPIDEMIOLOGY

Coronary artery disease (CAD) is a major worldwide public health problem. (1). The age adjusted death rate is 165.67 per 100,000 of the population. (2) Coronary artery bypass surgery (CABG) is a surgical procedure opted to relieve uncontrolled angina, prevent or relief left ventricular failure, thereby reducing the risk of death. (3). Grafts are used to restore normal blood flow to ischemic myocardium through a CABG across the obstructed coronary artery in patients having advanced CAD.

In 2015, stroke was the second most frequent cause of death after CAD, accounting for 6.3 million deaths (11% of the total).

For every 100 strokes destined to happen, approximately 20 will be hemorrhagic and 80 will be ischemic (4). Out of 80 ischemic strokes, 60 will implicate the carotid territory, while 20 will be vertebrobasilar. Half of the 60-carotid territory, ischemic strokes will not be due to extracranial carotid artery disease leaving approximately 30 patients whose stroke will be due to embolism and/or thrombosis of the extracranial internal carotid artery (ICA).

In an ischemic stroke **(*image 1*),** blood supply to brain is impeded, leading to dysfunction or death of the brain tissue in that area. Thrombosis and embolism are main factors contributing to such an event. (5,6) Thrombosis can occur in a large or a small vessel; large vessel disease implicates the common and internal carotid arteries (ICA), the vertebral artery, and the Circle of Willis, while the small vessel disease implicates smaller arteries within the brain parenchyma itself. The source of more than 75% of strokes ***(image 2)*** related to extra-cranial large vessel disease is resulting to be ICA. (7)

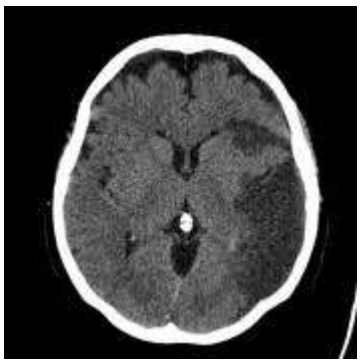


Image 1. CT brain scan reveals the ischemic territory, due to loss of blood supply.

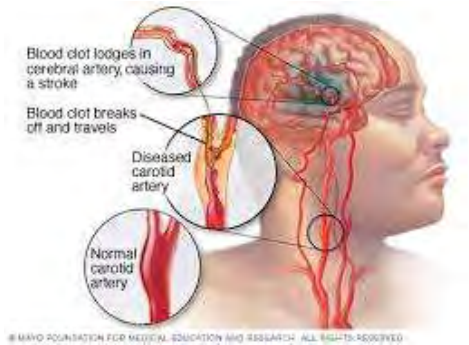


Image 2. Embolic clot generated by a stenotic carotid artery.

The ruinous sequence of stroke and CABG creates a significant medical state.

Stroke was a well-described post-operative complication after CABG in the 1960s (5% to 9%), but it remains one of the most calamitous post-operative complications. The advancement of the surgical techniques and the cardioplegia, the lessen of the procedure time and the expanded usage of statins and antithrombotic drugs, resulted in significant reduction of the stroke rate. Nevertheless, even in the modern era of the cardiovascular surgery, there is a residual stroke rate after CABG (1.3% to 2%.) (7). This adverse event has a pernicious impact in overall mortality (***image 3)*** morbidity, nevertheless a gargantuan socioeconomic cost.

Four out of ten of the strokes will eventuate during the procedure, and risk of postoperative stroke up to the first two days after surgery (mean time 40 hours) (8). The main pathogenesis for intraoperative stroke is embolic. Other causes (in waning sequence) includes surgical and clinical aspects which are mainly condensed in the pathophysiology of hypoperfusion. Irrespective of the etiology, strokes mainly are observed during the first post-operative day (9,10).

The incidence of fatal strokes follows a parallel course with the ageing of the patients, and it ranges from 8% among patients age <60 years up to 43% in octogenarian patients. The patients that experience a perioperative stroke as compared with patients without stroke, have an increased mortality risk by 2.2 times. Of note, the occurrence of stroke in the first month after surgery is associated with almost 13 times increased risk of stroke-related death. (11)

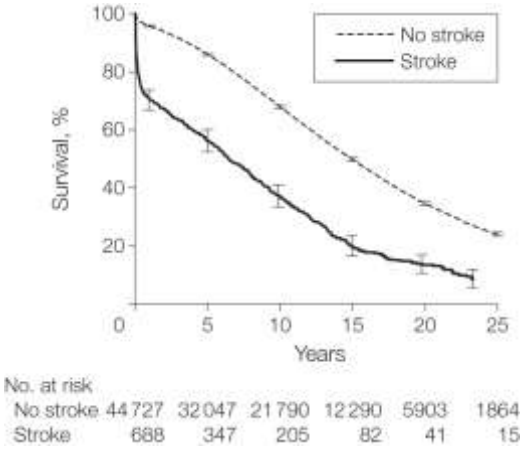


Image 3. Declined survival due to stroke after CABG. (67)

Chapter 2. ANATOMY-PATHOPHYSIOLOGY-PATHOGENESIS OF THE VULNERABLE PLAQUE

1. ANATOMY (*image 4*)

Occlusion or hemorrhage of the vessels supplying the brain, provokes symptoms that correlates anatomically with the affected brain area. Carotid arteries (CA) traverse the neck bilaterally and provides oxygenated blood ang glucose the brain.

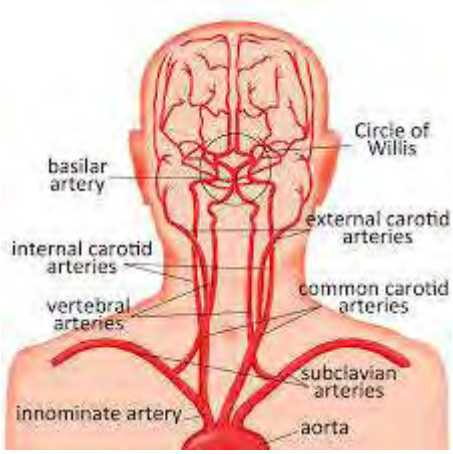


Image 4. Anatomy of the ascending aorta, aortic arch and carotid system.

2. PATHOPHYSIOLOGY (*image 5)*

Carotid artery (CA) disease is an aspect of cardiovascular disease (CVD), which is a consequence of atherosclerosis and atherothrombosis. Oil particles, cholesterol, calcium and some other substances interfere with the smooth muscular cells in the artery wall leading to plaque formation. The high on foam-cells plaques expand in volume gradually through the wall or to the lumen (positive remodeling) or they may cause clotting in an acute setting and lead in complete occlusion of the vessel. (12)

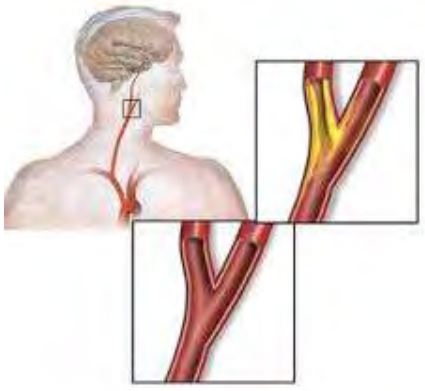


Image 5. Atherosclerosis of the carotid artery leading to stenosis.

3. THE VULNERABLE PLAQUE *(image 6)*

Most plaques start on the outer wall of the proximal ICA where there is an area of low shear stress. In a process termed “positive remodeling”, the proximal ICA initially expands (rather than becoming stenotic), before the atheromatous plaque starts to compromise the vessel lumen. Key pathological features in the development of the more complex carotid plaque include progressive inflammation, lipid accumulation, apoptosis, proteolysis and angiogenesis. (13) Activated macrophages, T cells and mast cells are more prominent in the plaques of patients with recent symptoms and they release matrix degrading enzymes (e.g. the active form of matrix metalloproteinase) which cause erosion of the extracellular matrix of the fibrous cap that overlies the lipid rich necrotic core, as well as producing a variety of other growth agonists and antagonists and pro-/anti-inflammatory cytokines. (13) In addition, there is increasing neo-angiogenesis of the plaque and increasing apoptosis of smooth muscle cells. (14). That leads to fibrous cap rupture or plaque ulceration, which exposes the inner core to over-lying thrombus formation, distal embolization and onset of symptoms.

The principle characteristics of a stable (versus unstable) carotid plaque include: 1) a fibrous vs atheromatous pathological process 2) thick fibrous cap vs a thinned cap 3) a small lipid rich core vs a large core 4) increased collagen levels vs reduced collagen 5) increasing calcification vs no calcification 6) no overlying plaque ulceration vs evidence of ulceration 7) no intraplaque hemorrhage vs intraplaque hemorrhage 8) no inflammatory cells vs increasingly macrophage rich plaques and 9) a higher proportion of smooth muscle cells vs low levels in unstable plaques. (13,15)

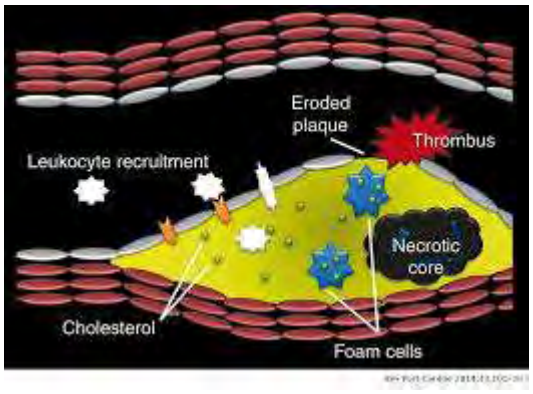


Image 6. Infiltration with foam cells of a vulnerable plaque.

Chapter 3. IMAGING MODALITIES

The visualization and orientation of the stenotic arteries that may generate embolic events is a sinequanone principle during the process of risk stratification, peri-operatively.

1. DIGITAL SUBTRACTION ANGIOGRAPHY (DSA) *(image 7)*

Angiography is accepted as the gold standard for the visualization on the vessel course (92.6% sensitivity and 97% specificity). (16) On the other hand, the invasive character (puncture of the peripheral artery) and risk of complications (bleedings, hematomas, infections), lead to replacement by other less invasive methods, with only exception the below-the-knee arterial disease. This exam can be used in the case of discrepancy between non-invasive imaging tools.

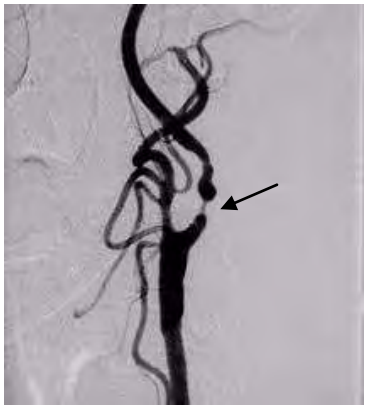


Image 7. Conventional angiography of the right internal carotid artery.
Arrow: significant stenosis (90%).

2. DUPLEX ULTRASONOGRAPHY (USG) *(image 8 and 9 and 10 and 11)*

USG is the most sensitive and accurate modality in order to evaluate the morphology of CA and trace stenosis or other anomalies. The methology of studying the vascular structures is based on the physics of sound waves, which offers hemodynamic data of the carotid and vertebral arteries. Visual information of the plaque has additive value. Gronholdt et al. (17) referred that in a mixed population of 111 asymptomatic and 135 symptomatic carotid stenosis patients (with stenosis > 50%) which has been followed for a period of 4.4 years, echo-lucency of plaque was of predictive significance, regarding on the risk of stroke, and this continuum elevated with the percentage of the stenosis.

The Gray-Weale Classification is based upon the echo-lucency/echogenicity of the plaque and has five sub-types. (18). Whilst, quite subjective as categorization, increasing plaque lucency is associated with a greater prevalence of “soft” tissue plaques on histological examination (defined as any combination of hemorrhage, lipid core or any other “soft tissue constituents”). Using this simple technology, the Cardiovascular Health Study Group (19) demonstrated that during follow-up patients with echo lucent plaques faced a significant increase of risk of ipsilateral stroke.

The evaluation via the echo-Doppler, is performed with the usage of a probe at a frequency of 7.5 Hz. The Echo-Doppler scanner combines a B-mode ultrasound imager with a pulsed Doppler flow detector to estimate flow velocities at specific location in the visualized artery. This system can also permit to place a sample volume in the vessel under study and the angle of incidence, which is kept as near to 60^{o} as possible, to be measured. By using the measurements of flow-velocity, the Echo-Doppler scanning has a sensitivity and a specificity of >90% and >80% respectively to detect hemodynamically significant carotid stenosis.

B-mode images are taken from the video and normalized for the grey scale by the use of linear scaling with luminal blood (grey scale “0”) and the adventitia (grey scale “190”). Having normalized the image, it is possible to calculate the median “greyness” of the plaque (the Grey Scale Median [GSM]) using computerized software. (20) This allows a more objective means of evaluating plaque lucency and echogenicity, providing even prognostic information, nor only diagnostic.

In the modern era of 3D imaging, the better and earlier visualization of ulceration may play important role, since ulceration carries a 3-fold higher risk for stroke, based on previous studies with angiography (NASCET trial, 21)

Since the resolute ability of ultrasound is greater than that of MRI or PET scanning, it is possible that in the future, 3D ultrasound will be method of choice for the detection of ulcers, scars and other lesions that affect the wall surface.

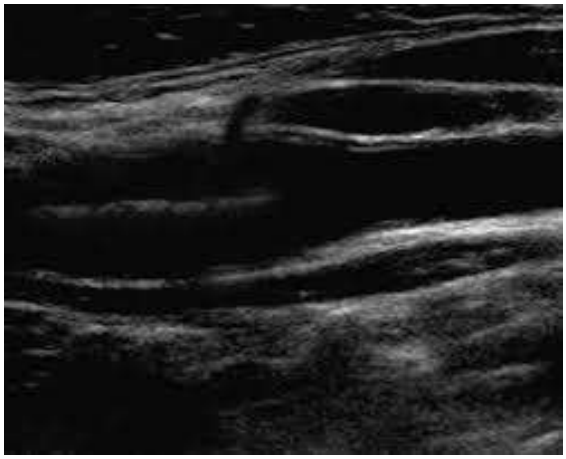


Image 8. Patent carotid artery. Gray-scale evaluation of the wall.

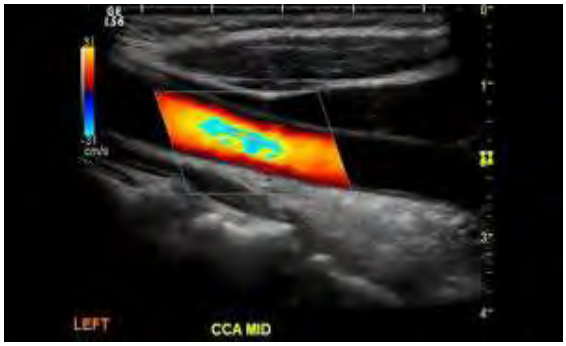


Image 9. Normal blood flow of the left common carotid artery.

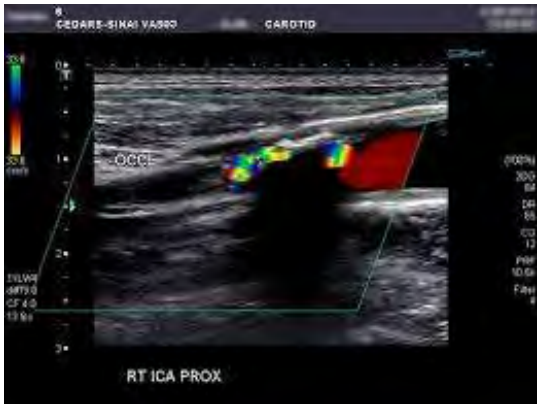


Image 10. Carotid artery stenosis.

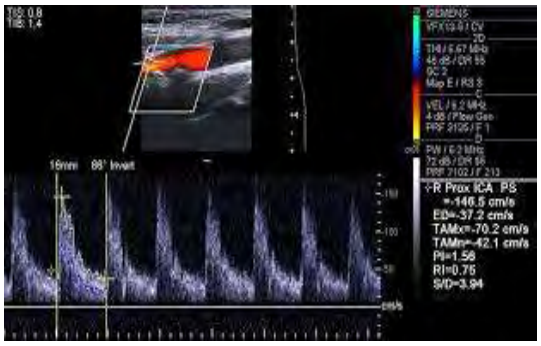


Image 11. Increased velocity through the stenotic area.

3. TRANSCRANIAL DOPPLER MICROEMBOLUS DETECTION

The detection of micro emboli by transcranial Doppler (TCD), is probably one of the best validated method to detect high risk patients for stroke. The detector is placed on the head, and the patient is evaluated through monitoring to detect micro emboli. Once the emboli passes through the circulation, there is a popping or clicking sound, and it can be seen on the screen of the device. In 2010, Markus et al. (22) at the Asymptomatic Carotid Emboli Study (ACES), managed to highlight the significance of the micro- emboli detection, as a major element at the recognition of the high-risk patients. Of 467 patients with prior history of ACS, with examined TCD files, embolic signals were observed in 77 (16.5%) at baseline. When referring to ipsilateral stroke, the hazard ratio was 5.57 (1.61-19.32; p = 0.007). The absolute annual risk of ipsilateral stroke or TIA at 2 years was 7.13% in patients with embolic signals and 3.04% in those without. Referring to ipsilateral stroke the annual risk was 3.62% in patients with embolic signals and 0.70% in those without. Spontaneous embolization in the middle cerebral artery (MCA) ipsilateral to a proximal ICA stenosis is a marker of an unstable plaque. The detection of spontaneous embolization is increased in symptomatic (versus asymptomatic) patients. (23)

4. EPIAORTIC ULTRASONOGRAPHIC SCREENING (EAS)

EAS is the preferred, easy, safe and effective modality offering greater accuracy in the assessment of ascending aortic pathology than both TEE and manual palpation. So, both STS and AHA, recommends the routinely use of EAS for the evaluation of presence, location and severity of a plaque in the ascending aorta in order to reduce the incidence of athero-embolic complications (Class IIa, level of evidence B).

5. COMPUTED TOMOGRAPHY ANGIOGRAPHY (CTA) (*image 12)*

CTA is a frontrunner among the imaging modalities due to its short examination time and the reduced amount of motion and respiration artefacts (lessen than MRA). Other advantages include fast non-invasive acquisition, broad availability, decreased cost, high resolution and 3D reconstruction ability (***image 13***). It sketches the entire vascular tree and provides valuable information at the planning of interventional strategies (lesion detection and evaluation of anatomy (i.e. linear, curly or wrap-around lesions), percentage of calcinosis, the proximal and distal vasculature). Pitfalls of CTA are mainly the inability to provide functional and hemodynamic data, due to his static character, the accompanied radiation and the need of iodinated contrast agents. The use of contrast agents is limited in patient with deteriorated renal function and in patients with known allergic reactions.

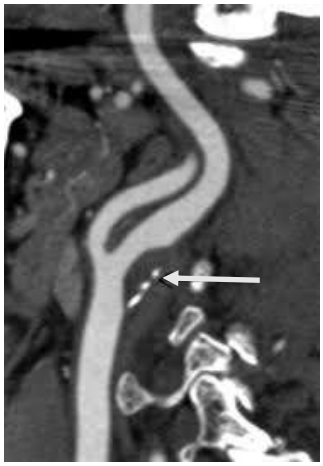


Image 12. CT angiography or the carotid system.
Arrow: significant stenosis and calcification.

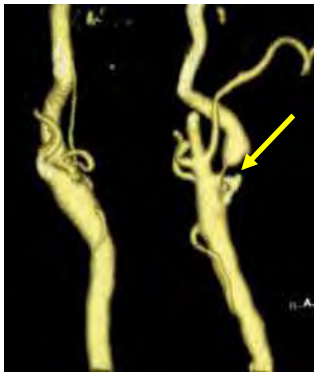


Image 13. 3D reconstruction of the carotid artery showing a significant stenosis of the internal carotid artery (arrow).

6. MAGNETIC RESONANCE ANGIOGRAPHY *(image 14)*

MRA is one of the leading imaging modalities for analyzing carotid plaque morphology. It uses gadolinium as contrast-agent, and no-contrast techniques (phase contrast and time-off-light sequences). It is a valuable alternative in patients with mild to moderate CKD.
In comparison with CTA, MRA does not need iodine contrast and has higher soft tissue resolution; from the other hand, motion artifacts are more frequent. The presence of pacemakers, implantable cardioverter defibrillators (ICDs), claustrophobia or severe CKD, are the main contraindications.

The American Heart Association (AHA) developed a classification for defining the complexity of carotid plaques which has been modified by adding an MRI based classification to match each category. (24)

MRI criteria have been developed for evaluating the status of the fibrous cap. (25). An intact (thick) plaque shows a continuous hypointense band near the bright lumen on 3D-TOF imaging in the presence of a smooth luminal surface, while the hypointense band is not visualized in an intact but thinned fibrous cap. A ruptured cap was defined as being present when there was absence or discontinuity of the hypointense band or a juxta-luminal hyperintense signal with the TOF and T1 weighted images consistent with a recent hemorrhage and/or an irregular luminal surface. Using MRI, there was 80% sensitivity and 90% specificity for diagnosing a thinned or ruptured fibrous cap. (25)

Data, mainly from small registries implicate that several characteristics of the vascular plaques such as large lipid-rich necrotic central core, diffuse micro- hemorrhage, thin fibrous cap and neo-angiogenesis can be detected by MRI. Of note, these visualized pathogenetic elements are of predictive significance for plaque erosion.

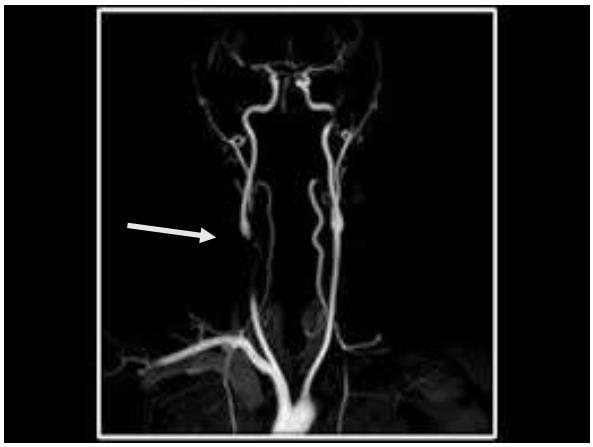


Image 14. MRA showing longitudinal stenosis of the left internal carotid artery.

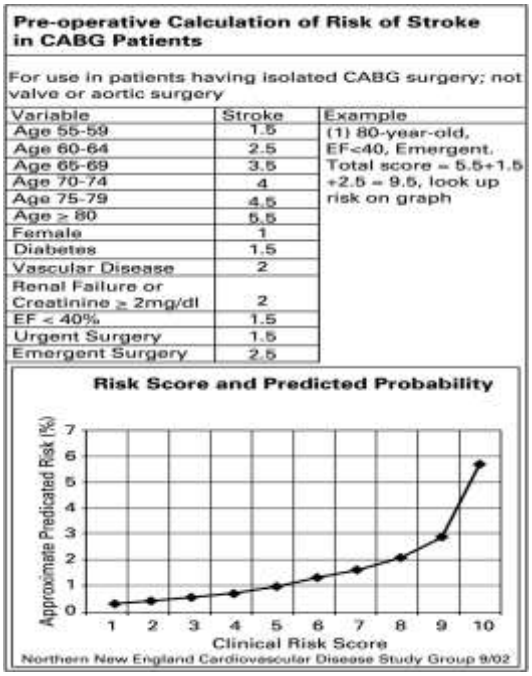
Chapter 4. RISK STRATIFICATION

The occurrence of a stroke at the peri-operative period carries a tremendous burden of morbidity, if not mortality, increases the total cost of hospitalization and affect the QUALYs of the patient, nevertheless the family support system. Consequentially, the identification of a frail patient at increased risk of stroke is of paramount importance during the surgical decision-making approach and informed consent, mimicking the importance of the Holy Grail.

Of importance, any elective procedure should be postponed until the holistic determination of the patient risk-profile is completed, with only acceptable exception the emergent status (i.e. rupture of a wall, severe symptomatic left-main disease with no option for interventional angioplasty), in order to avoid the calamitous consequence of a peri-procedure stroke event.

Several risk factors, which often co-exist, such as advanced age, arterial hypertension, diabetes mellitus type 2, atrial fibrillation, peripheral artery disease, renal insufficiency, left ventricular dysfunction and non-elective surgery have, repeatably been reported as activators of peri-procedural stroke. The combination of those variables has created many risk stratifications tools ***(image 15)*** that can be implemented before surgery, to determine the individual probability of stroke in patients undergoing CABG. (26). Data from the SYNTAX trial (27) that compared the 2 modalities of coronary revascularization (CABG vs. PCI), highlights the impact of common risk factors over the occurrence of peri-operative stroke ***(image 16).***

Hornero et al. (28) created and validated a new risk model (PACK2 score) (***image 17***), including priority of surgery, peripheral vascular disease, preoperative cardiac failure/left ventricular ejection fraction <40 % and chronic kidney disease. Interestingly, in patients with Pack2 score ≥2, off-pump CABG significantly reduced the risk of stroke compared with on-pump CABG, whereas in patients with PACK2 score <2, no big difference was appeared between the two strategies of revascularization. (26). Although this score outlines the additive effect of several variables that commonly co-exist, it fails to consider two important risk factors – atherosclerotic disease of the ascending aorta (29) and pre-existing cerebrovascular disease (30),factors, that should always be scrutinized. (26)



Pre-operative Calculation of Risk of Stroke in CABG Patients

For use in patients having isolated CABG surgery; not valve or aortic surgery

Variable	Stroke	Example
Age 55-59	1.5	(1) 80-year-old, EF<40, Emergent. Total score = 5.5+1.5 +2.5 = 9.5, look up risk on graph
Age 60-64	2.5	
Age 65-69	3.5	
Age 70-74	4	
Age 75-79	4.5	
Age ≥ 80	5.5	
Female	1	
Diabetes	1.5	
Vascular Disease	2	
Renal Failure or Creatinine ≥ 2mg/dl	2	
EF < 40%	1.5	
Urgent Surgery	1.5	
Emergent Surgery	2.5	

Image 15. Association of the combined variables and the predicted probability for the occurrence of stroke.

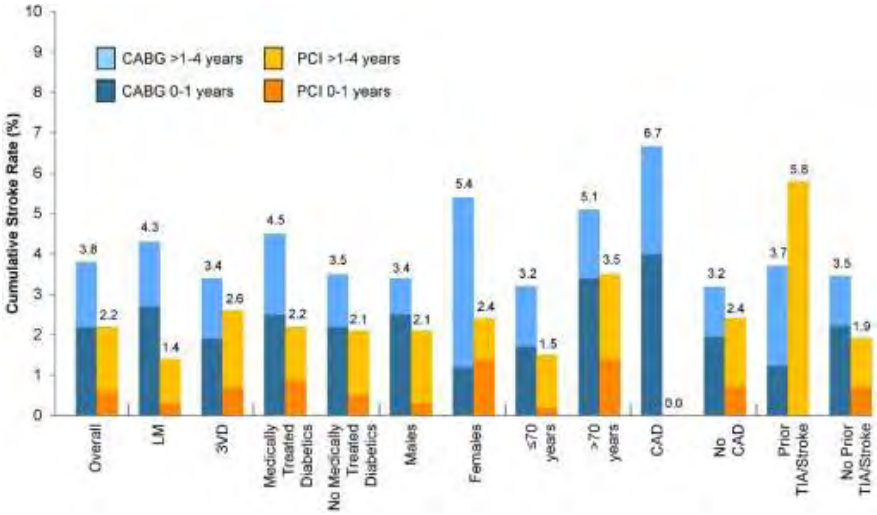


Image 16. Several variables that are associated with peri-operative stroke incidence.

Variable	$PACK_2$ score
Priority of surgery	
Non-elective	1
Elective	0
Peripheral arteriopathy	
Yes	1
No	0
Preoperative cardiac failure and/or LVEF < 40%	
Yes	1
No	0
Chronic kidney failure and/or preoperative creatininemia >2 mg/dl	
Yes	2
No	0

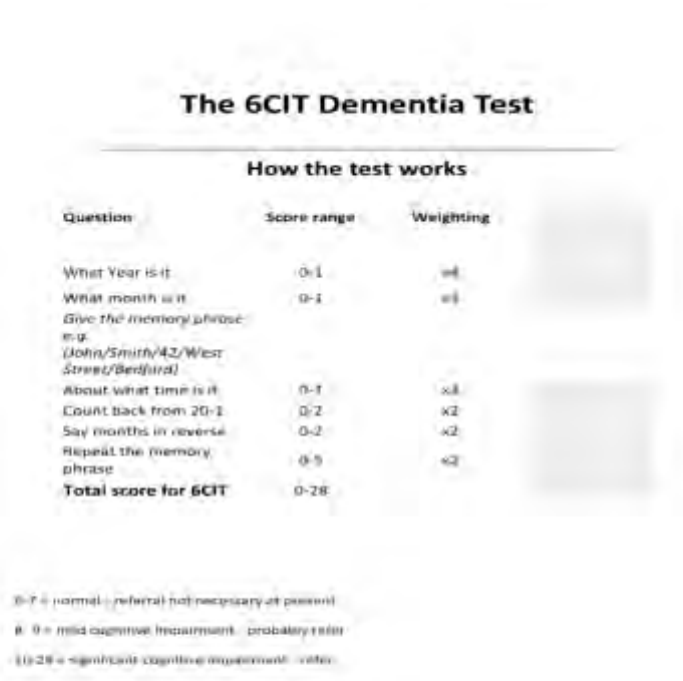
Image 17. Variables of the Pack2 risk score.

A brief demonstration of the more important risk factors is presented in the follow clauses, categorized as clinical, procedure-related, and miscellaneous.

❖ CLINICAL RISK FACTORS

Pre-existed neurological risk profile: Previous history of stroke/TIA is consistently the main predictor of peri-procedural stroke, in the bibliography.

- Any event of stroke (even transient episodes (TIA) should be recognized and reported via an extensive history record. This study implicates that patients with TIA are more likely to suffer a stroke peri-operatively than those without previous neurological symptoms (OR 3.35, 95% CI 2.38–4.71, p<0.0001). Even more emphatic, it was shown that CABG-patients with reported history of stroke had significantly higher risk to experience a new, or expanding stroke, when comparing with patients with either uneventful neurological history or previous history of TIA (OR 3.6, 95% CI 3.0–4.3, p<0.0001. (31)
- Recognize any neurocognitive disorders via validated questionnaires (e.g. 6CIT score (***image 18***), IQCOED).


The 6CIT Dementia Test

How the test works

Question	Score range	Weighting
What Year is it	0-1	x1
What month is it	0-1	x1
Give the memory phrase e.g. (John/Smith/42/West Street/Bedford)		
About what time is it	0-1	x1
Count back from 20-1	0-2	x2
Say months in reverse	0-2	x2
Repeat the memory phrase	0-5	x2
Total score for 6CIT	0-28	

0-7 = normal - referral not necessary at present

8 - 9 = mild cognitive impairment - probably refer

10-28 = significant cognitive impairment - refer

Image 18. 6CIT Dementia score. 6 simple questions that identify early signs of cognitive impairment.

- Recognize cerebral ischemia by MRI (even asymptomatic).

Aortic atheroma: The identification of moderate/severe atheroma is associated with the post-procedural stroke risk. Aortic atheroma may generate a thromboembolic event to the brain circulation, during several steps of the procedure (clamping, suturing, etc.) Computed tomography scanning, trans-esophageal echocardiography ***(image 19-20)*** or magnetic resonance imaging, can be performed before the surgery to evaluate the quality of the aortic wall.

The definition of significant aortic arch disease includes aortic wall thickening >5mm, on top of, either severe calcification or protruding/mobile atheroma or ulcerated plaque with presence of thrombus or circumferential involvement with laminated appearance. The existence of severe aortic disease is associated with remarked increase of the peri-operative stroke risk (5-19%) as compared with only 0–2% in patients without significant aortic arch disease.

Trans-esophageal ultrasonographic visualization of the aorta, during CABG, provides further information regarding the atherosclerotic changes in the entire ascending aorta, especially at the clamping and de-clamping steps (26). Of note, the only clinical predictor of severe aortic arch disease is a carotid bruit. (31)

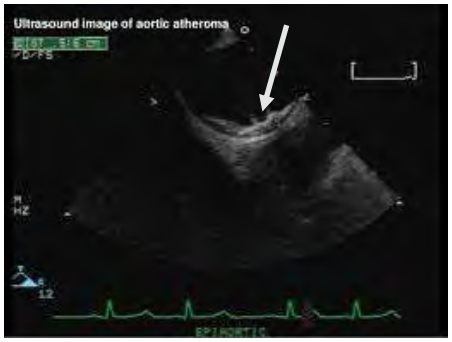


Image 19. Transesophageal ultrasound reveals the presence of aortic atheroma grade 4 (arrow) (atheroma> 5mm).

Grade	Severity (atheroma thickness)	Description
1	Normal	Intimal thickness < 2 mm
2	Mild	Mild (focal or diffuse) intimal thickening of 2–3 mm
3	Moderate	Atheroma >3–5 mm (no mobile/ ulcerated components)
4	Severe	Atheroma >5 mm (no mobile/ ulcerated components)
5	Complex	Grade 2, 3, or 4 atheroma plus mobile or ulcerated components

Image 20. Grade Classification of the Aortic Atheroma.

Carotid artery disease: As clinical entity, it may be eluded for many years. Unrecognized carotid disease is generally present in elderly patients who are asymptomatic (32). This registry demonstrated that significant (>75%) carotid artery stenosis was present in 11.3% of asymptomatic patients older than 60 years of age, who were screened with DUS before elective CABG. (33). Of importance the combined stroke/TIA risk advances with the percentage of the ipsilateral stenosis. 86% of the reported strokes occurred ipsilateral to a hemisphere without a 50–99% stenosis (critical stenosis) or total occlusion and only 7% of strokes/TIAs occurred ipsilateral to a surgically treated stenosis. (31). The risk increases further for patients with bilateral lesions even in the absence of symptoms, whilst in unilateral disease, even in the setting of extensive unilateral stenosis, the risk is ameliorated. This observation highlights the presence of bilateral lesions as a major contributor of strokes. Moreover, the zenith of risk was observed in patients with total occlusion. (31)

- **Presence of symptoms**

a. Asymptomatic carotid stenosis: It is generally accepted, based on the bibliography, that the presence of asymptomatic carotid stenosis is not an independent risk factor for ipsilateral carotid-area ischemic stroke after CABG (34,31). Of note, in other studies the presence of asymptomatic carotid stenosis of 50–99 % without prophylactic carotid revascularization pre-operatively; lead to zero perioperative stroke events (34,35,36). It can be deduced that the risk of perioperative stroke in CABG is slightly increased in patients with asymptomatic unilateral carotid artery stenosis. (10). In other words, the absence of symptoms is positively associated with the risk of stroke.

b. Symptomatic carotid stenosis: Symptomatic carotid artery stenosis uplifts the risk of a postoperative stroke. However, the bibliography has scarce evidence-based data appertained to this clinical entity. For that reason, the question whether prophylactic carotid revascularization could ameliorate the risk of CABG-associated stroke, remains unsolved. (10)

- **Percentage of occlusion**

In the bibliography, the term ‘‘severe stenosis’’ or ‘‘stenosis >50%’’ is correlated with a significantly increased risk of operative stroke. (31) The stroke risk in patients without severe carotid disease was 2.0% (95% CI 1.7–2.3) and raised up to 8.4% (95% CI 6.0–10.7) in patients with ‘‘a carotid stenosis >50%’’. Of note, in patients with 100% occlusion, Carotid Endarterectomy (CEA), is contra-indicated. If the data are re-analyzed and the patients are categorized as with: (i) no carotid disease, (ii) severe (50–99%) stenosis or (iii) total occlusion, the highest risk is now reported in the group of total occlusion. Patients without significant carotid disease had a 1.9% (95% CI 1.5–2.3) stroke-risk, which was elevated up to 6.7% (95% CI 2.5–10.8) in those with a 50–99% stenosis. The highest peri-operative stroke risk (11.5%, 95% CI 0.0– 23.9) is observed in CABG patients with at least severe occlusion. In other words, patients with a 50–99% carotid stenosis have a 4-fold time to suffer a perioperative stroke than patients with no significant disease (OR 3.6, 95% CI 2.0–6.5, $p<0.0001$). In case of carotid occlusion CABG patients have more probabilities to suffer a stroke than patients with an amount of stenosis

between 50 and 99% (OR 1.5, 95% CI 0.6–3.7, p=0.3394), but this did not reach statistical significance. (31)

The European Cardiology Society in the recent guidelines (38) ***(image 21)*** for myocardial revascularization (2018), emphasizes on the patient-profile that need to be screened for carotid artery disease.

Recommendations	Class[a]	Level[b]
In patients undergoing CABG, carotid DUS is recommended in patients with recent (<6 months) history of stroke/TIA.	I	B
In patients with no recent (<6 months) history of TIA/stroke, carotid DUS may be considered before CABG in the following cases: age ≥70 years, multivessel coronary artery disease, concomitant LEAD, or carotid bruit.	IIb	B
Screening for carotid stenosis is not indicated in patients requiring urgent CABG with no recent stroke/TIA.	III	C

Image 21. ESC Guidelines 2018: Myocardial revascularization. Screening of carotid disease pre-operatively.

<u>Carotid revascularization:</u>

There is no evidence that the strategy of prophylactic revascularization with either endarterectomy or stenting ***(image 22 and 23)***) in unilateral asymptomatic carotid stenoses in CABG candidates reduces the risk of perioperative stroke. (37) The words unilateral and asymptomatic when co-exist at the evaluation of the patient's profile, are assumed to be of diminished clinical importance and do not justify any intervention before the CABG.
It may be reasonable to restrict prophylactic carotid revascularization to patients at highest risk of postoperative stroke, i.e. patients with severe bilateral lesions or a history of prior stroke/TIA. Hence, the indication for revascularization, and the choice between carotid endarterectomy or carotid artery stenting in these patients, should be made by a multidisciplinary team including a neurologist.

- In patients, scheduled to CABG, with recent (< 6 months) history of TIA/stroke, carotid revascularization should be considered in stenosis 50-99%, [**IIa, LoE B]**, while is not recommended in stenosis <50%. [**III, LoE C]**
- In patients, scheduled to CABG, with asymptomatic carotid disease, carotid revascularization should be consider in bilateral stenosis 70-99%, or in the setting of other high risk triggers for ipsilateral stroke (i.e. contra-lateral TIA/stroke, ipsilateral silent infarction areas on imaging, intra-plaque hemorrhage or lipid-rich necrotic core on MRA, or any of these findings on ultrasound: gradual progression of the stenosis degree (>20%), spontaneous embolization, visualized on transcranial Doppler, impaired cerebral vascular reserve, excessive plaques, echo lucent plaques, or increased juxta-luminal hypoechogenic area) [**IIb, LoE C]**.

On the contrary carotid revascularization is not recommended as prophylactic strategy in asymptomatic patients [**III, LoE C]**

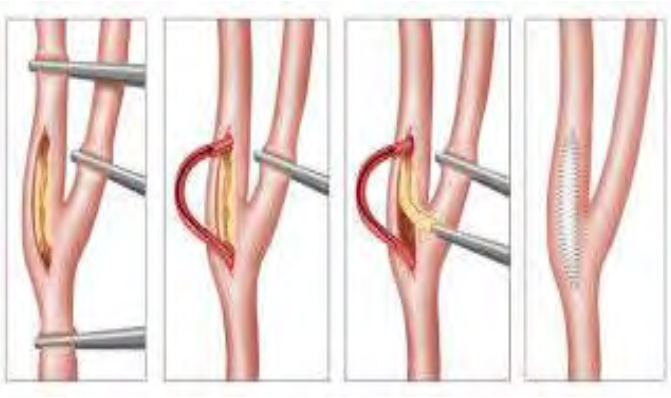


Image 22. Carotid endarterectomy (CEA).

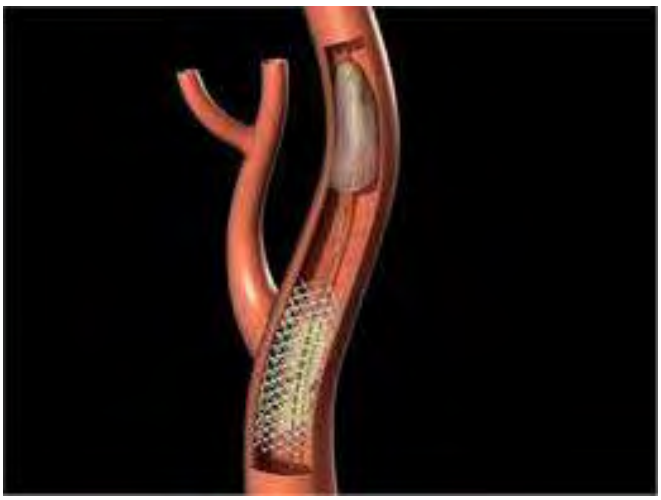


Image 23. Carotid stenting.

<u>Myocardial infarction</u>: Mooe et al, (39) reported an increased incidence of stroke after recent myocardial infarction. Potential reasons are the hemodynamic instability, the hypokinetic walls of the ventricle, the increased blood thrombogenicity, and the pronounced sympathetic activation. Common comorbidities, such as chronic renal insufficiency, compressed ejection fraction, diabetes mellitus may increase further the thrombogenicity, leading to thrombus formation inside the left ventricle (***image 24 and 25***) which could provoke a systemic embolic event via carotid system to the cerebral arteries. This is well visualized through echo-ultrasound, which unveils the “sludge” (thin thrombus). Of note Multi-vessel disease is also associated with a post-CABG neurologic event. (40)

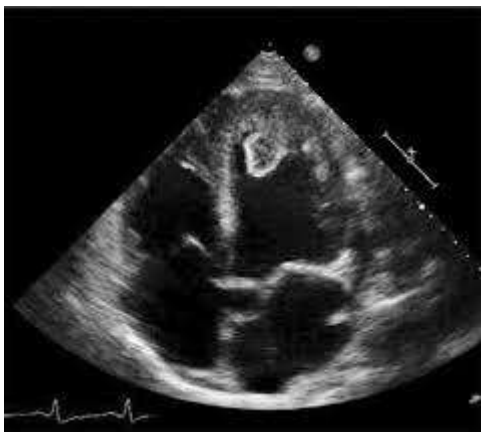


Image 24. Trans-thoracic ultrasound. Thrombus attached to the left ventricular apex, which is akinetic due to anterior STEMI.

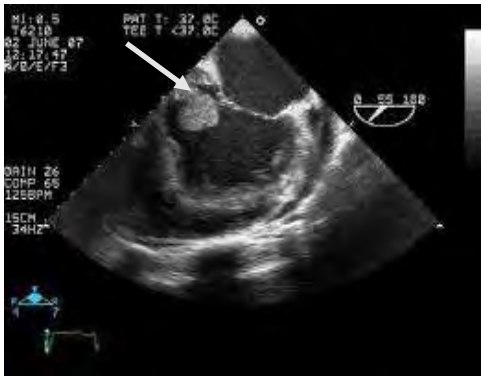


Image 25. Trans-esophageal ultrasound. Thrombus attached to the intraventricular wall as a result of impaired contractility of the left ventricle (arrow).

Low ejection fraction: Either as a consequence of prior coronary syndrome, myocarditis, dilated myocardiopathy or as a result of a failed surgery, low cardiac output post-operatively is doubles the risk of stroke (41), for the same reasons that are described above.

Atrial fibrillation: 1 out of 3 patients with heart disease has also atrial fibrillation (AF), a clinical entity that is associated with increased thrombogenicity per se. This risk factor is usually well recognized before the surgery, as part of the cardiology evaluation of the patient, and thereby more controlled. Given the fact that antithrombotic therapy is generally discontinued perioperatively, to minimize the bleeding risk, the patient is exposed to increased thrombotic status. On the other hand, even new-onset AF (or post-operative AF i.e. POFA), resulted in higher postoperative stroke incidence. POFA is present in 16–30 % of patients in the early postoperative period (first 5 days) post- CABG (42,43). Usually these episodes occur by day three (44). In this meta-analysis by Megens et al (45), failed to detect male sex as significant contributor. The adverse effects of NOAFs are in line with the results of NOAF occurring in the context of other cardiac surgeries. One meta-analysis of patients who had undergone CABG detected a similarly increased NOAF-associated long-term mortality risk (odds ratio 2.19, 95% CI, 2.14–3.08) at 1-year follow-up. (46)

Chronic Obstructive Pulmonary Disease (COPD): This clinical entity is associated with controversial study results. In contrast to other studies, the presence of COPD was not recognized as a trigger for post-CABG stroke, Although hypercapnia (main component of COPD) may interfere with the cerebral vasoreactivity, which could contribute to the total stroke risk, this pathogenetic mechanism does not translate into a net clinical event. Of note, there may be a selection bias since is relatively common that patients with severe COPD are not favorable surgical candidates, leading to a mis-represented population. This could be the explanation why COPD is not considered a risk factor for postoperative stroke or mortality. (11)

❖ PROCEDURE-RELATED RISK FACTORS

Embolism: Four types of arterial embolism can occur during cardiac operations, based on the embolic substance: thromboembolism, atheroembolism, air embolism and less often, embolism of chronic vegetations that dislocate from the valves or the aortic wall. Embolic strokes associated with CABG are predominantly of thrombotic and atheromatic origin. The embolic component is disengaged from aortic plaques during the manipulation of the clamping/de-clamping of the ascending aorta. The turbulent high-velocity blood flow from the aortic cannula eases the dislocation of the embolic material whereas another source may be the proximal graft anastomoses in the ascending aorta.

Type of procedure: Moody et al, (47) based on pathological evaluation of the brain tissue after conventional (on-pump) CABG, detected multiple emboli lodged in small cerebral arterioles and capillaries, causing total occlusion and hereby harvest of the area. Additionally, in this prospective study by BhaskerRao et al, on-pump CABG was associated with increased cerebral dysfunction, when compared with cases of off-pump surgeries. CABG without cardiopulmonary bypass as strategy should further be evaluated, orientated as smoother- technique on the brain function. This approach may highlight a possible indication of the off-pump procedure in patients with carotid artery disease or other high-risk characteristics for stroke. (41). Conservative hypothermia (range of 32^{o}C) is commonly used during procedures under cardio-pulmonary bypass, based on the hypothesis that systemic hypothermia may act protectively against transient cerebral ischemia, due to reduced cell metabolism. Re-warming should be gradual in order to avoid the increased risk of neurologic injury of hyperthermia. The optimum blood pressure in order to eliminate the neurological complications, is unknown. In this trial, patients undergoing CABG were randomly allocated to a higher mean arterial pressure (80–100 mmHg) and they experienced fewer neurological adverse events, when compared with patients in the lower mean arterial pressure group (MAP) (49). Other studies also propose that the maintenance of an intra-operative MAP over 80 mmHg may ameliorate neurological complications. OPCAB (Off-pump) techniques mainly attenuate the amount of emboli which is generated by the disruption/erosion of atheromatous plaques during cannulation, cross-clamping and manipulation of the ascending aorta. Large retrospective studies have reported that OPCAB lead to a lessen incidence of stroke in contrast to conventional on-pump CABG ***(image 26)*** (50,51).

In the randomized ROOBY trial, which assigned 2203 patients to either on-pump or off- pump procedures, no difference between the two groups in stroke rate was reported. (52,10)

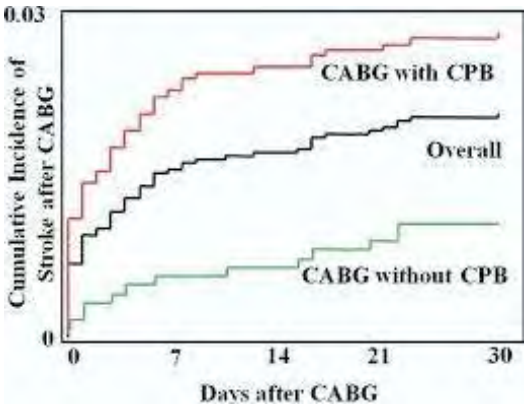


Image 26. Reduced cumulative incidence of peri-operative stroke during off-pump surgery.

Cerebral hypoperfusion: Intraoperative hypotension (an essential compound of the procedure) and declined cardiac output contribute to global cerebral hypoperfusion. The reduced blood flow during surgery may result in diminished katharsis (washout) of embolic materials from systemic vasculature. This adverse event is mainly seen in watershed areas around the borders of major arterial territories and provokes ischemia (53,10). On the other hand, even prolonged recovery time from anesthesia might also have contributed towards such events. (54)

Cross-clamp time: Most cerebral emboli, are observed immediately after the aortic cross clamping step, and at the time of aortic clamp removal (air- emboli or atheromatous). In this study, cross-clamp time was significantly higher in the group that experienced postoperative stroke (46619 minutes for stroke patients vs. 42625 minutes for no-stroke patients, $p< 0.001$). (41)

Overall cardiopulmonary bypass time: When prolonged, is associated with higher incidence of stroke (in total: 77659 minutes for stroke patient vs. 67640 for event-free patients, $p<0.001$). The optimum duration of the procedure may be attenuated only to 120 minutes. (41)

Number of proximal anastomoses: It is related with increased stroke risk (2.761 vs 2.461, respectively; $p<0.001$). (41) Royse et al, propose the technique of epiaortic scanning plus Y- graft, (the radial artery is anastomosed to the left internal mammary artery in a Y-graft mode) since they reported a significantly lower presence of cerebral embolization, secondary to aortic instrumentation.

Prostacyclin infusion: Based on older studies, this intra-operative practice during, may diminish the risk of encephalopathy and stroke, by blocking the adhesion of platelets to the extracorporeal tubing, decreasing the proportion of micro-embolic events in the cerebral tissue. (41,55). Current guidelines do not propose this prophylactic option.

❖ MISCELLANEOUS RISK FACTORS

Age: As an axiom, stroke risk increases with age. In patients aged <50 years the risk is <0.5%. This percentage raises exponentially up to 1–1.5% for patients aged 50–60, 2–3% for those aged 60–70, 4–7% for those aged 70–80 and up to 8–9% in octogenarians. Since the proportion of elder patients, that are leading to the operation room, has increased, age is characterized as unremitting risk factor, per se. Nevertheless, aging accompanies other risk factors, such as heart disease, carotid disease, diabetes etc, increasing the total frailty profile of the patient.

Smoking: Current smoking status increases thrombogenicity, platelet re-activity and adhesion and may lead to plaque erosion. Thus, it is a well addressed and most importantly, a modifiable risk factor.

Left atrial appendage *(image 27)*: This anatomic structure may generate the formation of thrombus and is associated with increased risk of spontaneous embolic strokes. Closure devices are may be used interventional, although more commonly, the appendage is removed surgically during the CABG.

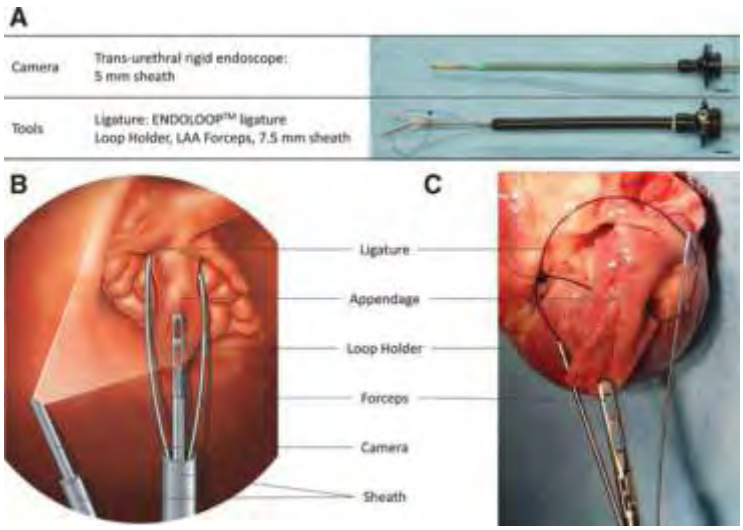


Image 27. Surgical excursion of the left atrial appendage, during CABG.

Pharmaceutical agents: The optimum medical therapy as preventive tool of stroke is based on the axon of statins and the axon of antithrombotic (antiplatelets and/or anticoagulants)

a. Statins: They reduce the levels of low-density lipoprotein (LDL)-cholesterol (C) and improve plaque volume and composition. It has a well-established benefit over long-term mortality in patients with coronary heart disease, including those undergoing CABG. The majority of CABG-patients already have a guideline-based indication for long-term statin therapy with strict target goal <70 mg/dl for LDL value. The usage of statins pre-operatively is associated with a significant reduction in the risk of post-operatively atrial fibrillation (POFA)(24.9 vs. 29.3 %, $p<0.05$) and stroke (2.1 vs. 2.9 %, $p<0.01$) (56). Several observational and randomized trials (57,58) have demonstrated that administering statins before CABG decreases also the risk of perioperative mortality and stroke and ameliorates the systemic inflammatory response. Also with the use of atorvastatin has been referred an increase of the number of circulating early endothelial progenitor cells both preoperatively and postoperatively (59,60). A recent meta-analysis (61) of preoperative statin therapy trials confirmed that the use of statin decreases not only the incidence of POFA, but also stroke and mortality. Of interest, the treatment with statins can significantly reduces hospital LOS (length of stay) after CABG. (60). Rosuvastatin ameliorated carotid stenosis in the ASTEROID study (62) and altered the composition of plaque. Targeting LDL< 70mg/dl in carotid artery disease, may stabilize the plaque and ameliorate the post-operative course. Based on the iconic Jupiter trial (63), rosuvastatin reduces by more than half the incidence of ischemic stroke among men and women with low levels of low-density lipoprotein cholesterol levels who are at risk because of elevated levels of high-sensitivity C-reactive protein.
b. Antiplatelets: The role of antiplatelets and especially the induction of aspirin (which is used in the majority of those patients due to the underlying coronary disease), carries the aura of an axiom. But whether aspirin directly decreases the risk of postoperative stroke remains a controversial issue. In this prospective observational study (64) which included more than 5000 patients, 60% of patients received aspirin within 48 hours post-CABG, and this therapeutic approach was associated with a significant reduction in stroke during hospitalization (1.3 vs. 2.6 %, $p<0.05$). Nevertheless, the surgeons are strongly motivated to initiate small dose of aspirin (i.e. 100mg) 6-24 hours post-operatively.
   The usage of clopidogrel in established carotid artery disease is well evaluated.
c. Anticoagulants: The presence of vascular disease adds 1 point in the CHADSVasc score, while history of TIA/stroke 2 points, highlighting the importance of adequate antithrombotic therapy. Bridging therapy with heparin perioperatively may decrease the bleeding risk but does not eradicate the thrombotic burden. For that reason, as soon the hemostasis is gained, based antithrombotic therapy must be re-initiated
d. The administration of beta blockers, sotalol, amiodarone, or antioxidant vitamins correlates with reduced risk of postoperative atrial fibrillation (65,66), and as a sequalae the lower incidence of POFA leads to lower incidence of stroke.

Chapter 5. CONCLUSIONS

Peri-operative stroke remains the most calamitous complication after CABG, adding burden of morbidity and mortality in a high-risk population by per se. Based on bibliography, despite the fact that data from randomized clinical trials are limited; several risk factors are highlighted, with headsman the presence of previous TIA or stroke. This observation emphasizes the role of symptoms at the evaluation of the risk profile of the patient who will undergo CABG. Other predisposed triggers are the extension of the cardiopulmonary bypass time, atherosclerotic lesions on the aortic arch or carotids, atrial fibrillation, coronary artery disease especially if there is reduced ejection fraction as a confound, diabetes mellitus and smoking, prior history of cardiothoracic surgery or CEA, the presence of thrombus on the apex of left ventricle, peri-operative hypoperfusion status (anemia, hypotension, decreased cardiac output). The presence of this extend heterogeneity (31), not to mention the inter-linked triggers, indicates that the stratification of the risk-profile of these patients is arduous but also grievous.

Preoperative Doppler study should be performed in candidates for CABG, based on clinical characteristics, in order to diagnose asymptomatic carotid disease, confirm the patency of subclavian arteries and stratify operative risk and prognoses.

Beyond the imaging aspects, the clinical risk profiling oriented to identify high-risk patients may be a better approach instead of a non-selective duplex screening and seems more logical and cost-effective, avoiding unnecessary examinations. (40)

During the procedure, several strategies may eradicate the risk of stroke such as the maintenance of hypothermia and adequate systematic mean arterial pressure, aiming in systemic euvolemia. The strategy of intra-operative monitoring via trans-esophageal or epi-aortic ultrasound is useful to identify early and adequately, mobile atheromatous plaques, which carry a high risk of dislocation and permits the selection of appropriate aortic manipulations. Of interest, there are two opposite opinions regarding the choice of off-pump CABG; one proposes it as an option for the prevention of stroke while the other forges against it as an ineffective aspect. (10)

Pharmacotherapy that includes statins, preventive and targeted medication for atrial fibrillation, or antiplatelets are of high importance. The effort to decrease the incidence of the post-operative stroke with a lone countermeasure is a chimaera. For that reason, sustained effort should be orientated in a multi-disciplinary approach of the high-risk patient using clinical and imaging tools. (10)

Scrutiny of the risk factors that are associated with increased prevalence of post-operative stroke is sinequanone. Efforts should be orientated on modifiable risk factors, for example, lipid profile, smoking counseling, procedural techniques or maneuvers, in order to eliminate the unavoidable residual embolic burden.

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