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Cerebrovascular events after cardiovascular surgery: diagnosis, management and prevention strategies

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Abstract

Introduction: Cerebrovascular events after cardiac surgery are among the most serious complications, related to a greater risk of patient mortality. This problem can occur following the formation of gas emboli during open heart surgery.

Aim: To address all the mechanisms that can lead to embolic events after cardiovascular surgery, how to manage them and how to possibly prevent them.

Material and methods: A search of the PubMed database was conducted. We reviewed the clinical literature and examined all aspects to identify the root causes that can lead to the formation of emboli.

Results: Among the studies reviewed, it was found that the main causes include manipulation of the aorta, inadequate deaeration after cardiac surgery, and blood-component contact of extracorporeal circulation. It has been reported that gas emboli can lead to deleterious damage such as damage to the cerebral vascular endothelium, disruption of the blood-brain barrier, complement activation, leukocyte aggregation, increased platelet adhesion, and fibrin deposition in the microvascular system.

Conclusions: Stroke after cardiovascular surgery is one of the most important complications, with a great impact on operative mortality and patient survival. Efforts have been made over time to understand all the pathophysiological mechanisms related to this complication, with the aim of reducing its incidence. One of the goals should be to improve both the surgical technique and the perfusion modality and minimize the formation of air bubbles or to facilitate their elimination during the cardiopulmonary bypass procedure.

Key words: stroke, early stroke, delayed stroke, gas microemboli, transcranial Doppler ultrasound, systemic inflammatory response syndrome.

Introduction

Stroke is a devastating complication that can occur after a cardiovascular procedure, negatively affecting survival and quality of life. Over time, strategies have been developed to reduce the incidence of stroke after coronary artery bypass grafting (CABG), valve surgery or carotid endarterectomy. With new technologies (stenting, transcatheter aortic valve implantation (TAVI)), the goal has always been to develop new strategies to reduce the risk of stroke [1].

Most strokes associated with cardiac procedures occur in the early postoperative period, confirming that they are directly related to the procedure. With a better understanding of risk factors and technological improvements, the incidence of stroke for surgical procedures and percutaneous interventions has significantly decreased [2].

CABG intervention is linked to a stroke risk of between 1% and 5%. A Society of Thoracic Surgeons database report reveals a decreasing incidence of stroke from 1.6% in 2001 to 1.2% in 2009. Stroke incidence is 1.5% for isolated aortic valve surgery, 2.1% for isolated mitral valve replacement and 1.4% for mitral valve repair. Stroke rates after isolated bicuspid aortic valve replacement, bicuspid valve and ascending aorta, root and ascending aorta, and complex arch replacement with circulatory arrest were 0.27%, 0.75%, 1.4%, and 0.8% [3].

Of fundamental importance is the analysis of the risk factors.

The risk factors are: advanced age, a previous stroke, previous cardiac surgery, atrial fibrillation, poor left ventricular function, previous carotid artery stenosis and peripheral vascular disease.

Most strokes associated with CABG occur in the perioperative period and are the ischemic type.

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Table I. Early and delayed stroke characteristics

Early stroke	Delayed stroke
Linked to intraoperative events	Related to post-operative AF or cerebrovascular disease
Independent of the patient's characteristics	Related to patient risk factors: previous history of stroke, hypertension, diabetes mellitus, old age, kidney disease, peripheral artery disease and cerebrovascular disease
Caused by aortic manipulation	Strong correlation with atrial fibrillation
Located in the right hemisphere	Located in the left hemisphere
Greater operative mortality	Negative impact on long-term survival

Stroke after CABG is likely caused by two factors: 1) Atheroembolic events, 2) Cerebral hypoperfusion

Atheroembolic events can be related to aortic cross-clamping, insertion and removal of the perfusion cannula, and construction of proximal graft bypass anastomoses.

Cerebral hypoperfusion may be a consequence of the increase of cross-clamp and cardiopulmonary bypass (CPB) times. For this reason, a surgeon's goal to reduce the risk of stroke may be to reduce aortic manipulation, clamping time, and extracorporeal circulation.

CABG has been shown to be superior to percutaneous intervention (PCI) in reducing death and myocardial infarction in patients with diabetes mellitus who have advanced coronary artery disease (CAD); but it has a higher risk of CABG-related stroke than PCI [4].

One strategy to reduce the incidence of stroke in periprocedural CABG has been to eliminate the need for aortic manipulation: the "aortic no touch" strategy. Fort this reason, we can use an off-pump CABG, exclusively using arterial ducts in situ (bilateral internal mammary arteries). This eliminates the need for aortic clamping and proximal aortic anastomosis. Another possibility is to perform a proximal anastomosis using the HEARTSTRING device, which has been shown to reduce the incidence of stroke.

When using extracorporeal circulation (on-pump CABG), a single cross-clamp is preferred because multiple clamps are associated with a > 2-fold increase in the incidence of neurological complications [5]. Another mechanism leading to periprocedural stroke is the formation of gas emboli during open heart surgery. Valve surgery requires adequate deaeration of the blood in the aortic root, atria, or ventricles to prevent air embolization. One option is the placement of a left ventricular catheter. Another option proposed was the flooding of the operational field with CO_2. CO_2 has been shown to reduce the risk of gas emboli formation. There is no evidence that a neurocognitive benefit exists in the use of CO_2 field flooding, but the results indicated a superior result in the treatment group [6].

New techniques are used such as minimally invasive aortic valve replacement and robotic mitral valve surgery. These new procedures carry a higher risk of stroke, compared with their conventional counterparts, although currently with better patient selection and more careful assessment of preoperative risk factors, the risk of stroke appears to be decreasing [7].

Epidemiology, characteristics and anatomic distribution

After cardiac surgery, the incidence of perioperative stroke is between 0.8% and 5.2% [8].

Stroke can occur during surgery or later.

We identify 2 types of stroke, with different pathophysiological mechanisms:

1. Early/intraoperative stroke (defined as detected "on awakening" or "after extubation") occurs mainly due to aortic manipulation and atheroembolism;

2. Delayed/postoperative stroke (defined as stroke that occurs after normal awakening from anesthesia) is usually related to postoperative atrial fibrillation or cerebral vascular disease.

Rates of early and late stroke were approximately ≥ 1% each. Both early and delayed strokes were associated with significantly increased operative and late mortality. The impact on operative mortality was significantly greater for early than for delayed stroke.

A previous history of stroke was associated more with delayed stroke, while off-pump CABG was inversely associated with early stroke [9].

The Table I shows the main differences between early and delayed stroke [10].

Early stroke is associated with a significant increase in operative mortality and reduced long-term survival.

Delayed stroke is associated with a previous ischemic event and has a negative impact on survival. The main strategies for the prevention of delayed stroke are AF prophylaxis, anticoagulant therapy and elimination of the left atrial appendage [11].

It is of fundamental importance to improve surgical results, to reduce the risk of both early and late stroke. It is necessary to know all the characteristics of these two types of stroke and to intervene to eliminate or reduce the patient's risk factors [12].

Understanding the mechanisms of stroke in heart surgery remains a challenge. Stroke may be a consequence of global hypoperfusion or embolic mechanisms. Stroke can be the effect of a single macroparticle or the result of the impact of numerous microemboli.

Knowing the hemispheric distribution of lesions is important, especially for understanding the possible mechanisms of stroke. The anatomical distribution of stroke injuries may reflect underlying mechanisms. Previous studies

have reported that early stroke in cardiac surgery had preponderance for the right hemisphere, as assessed by symptoms and verified by computed tomography (CT). Hedberg *et al.* [13] presented contradictory results with a predominance of lesions in the left hemisphere, presumably caused by jets of flow from the aortic cannula directing particles to the left hemisphere. Bilateral lesions were diagnosed in 30% of patients [13].

According to Ivascu *et al.* [14], early strokes were generally embolic in nature and localized in the right hemisphere, with involvement of the anterior circulation. In some cases, multiple distributions were observed. Late strokes often involved the left side and in rare cases involved both hemispheres, anterior and posterior [14]. Multiple distributions were found to be common in early strokes but not in late strokes, whereas late strokes tended to be more focal and more often localized in the left hemisphere. The strokes of the dominant hemisphere manifested with significant deficits, while non-dominant strokes were presented as clinically silent.

A stronger correlation was highlighted between late strokes and posterior hemisphere involvement, compared to early stroke. Posterior infarcts present with more subtle symptoms, such as ataxia or dysarthria. In these cases, late emboli are likely to be smaller in size and give no symptoms if they involve the anterior territory; but they become clinically evident if the posterior territory is involved [15]. An important aspect is the link between the patient's comorbidity and the onset of stroke. History of previous cerebrovascular events was highly predictive of early stroke, but not for events occurring after 24 hours. Early and late strokes are related to several risk factors. Preoperative risk factors for stroke can influence patient selection [16].

A recently published Canadian study supports the relationship between intraoperative blood pressure and stroke, highlighting how higher mean arterial pressures during CPB correlate with improved neurological outcomes [16].

Correlation between embolus size and brain damage: protection and monitoring

During CPB, gas microemboli can form. Manipulation of the vessels could lead to fragmentation of the atherosclerotic plaque and to the release of emboli. It has been suggested that the use of filtering systems can reduce the amount of solid or gaseous brain emboli [17]. To prevent microaggregates from embolizing the liver, kidney, lung, brain, and marrow, a number of filter elements are inserted into the ECC circuit. The filters are also equipped with anti-bubble devices to prevent gas embolism. There are 3 different locations: pre-bypass filters, on the crystalloid introduction or blood transfusion sets, filters between the cardiotomy and the oxygenator and filters on the arterial line, before the final return of blood to the patient.

Pre-bypass filters are used to decontaminate and debulk the circuit while circulating priming.

Micro-emboli form during cardiac surgery. These solid or gaseous emboli become particularly dangerous once they enter the cerebral circulation, causing silent heart attacks, strokes or death [18]. The study by Anyanwu *et al.* [19] shows that the incidence of stroke depends on the type of surgery; the incidence decreases to 1.7% if only patients undergoing CABG are considered. Many studies state that gas microemboli (GME) could be one of the causes of neurocognitive deficits after cardiac surgery [19]. The origin of emboli during cardiac surgery is difficult to identify, but two possible sources of GME are the heart-lung machine and blood-air contact at the surgical site. Air bubbles can be created at different stages of surgery, but it is unclear what the most threatening source is. An efficient method of preventing GME generation has yet to be found. There are strategies that can be implemented to reduce the amount of GME produced [20].

Dos Reis *et al.* [21] studied the use of the veno-arterial shunt. The use of this device can represent an alternative to controlling the production of gaseous microemboli during surgery; its use has been researched to reduce the inflammatory response caused by the passage of blood through the outer [21]. Cerebral embolism and cerebral hypoperfusion are the main causes of perioperative brain damage. There is a need to identify the factors involved in this mechanism, in order to reduce the risk of brain damage. From this goal arises the need to identify and develop neuromonitoring modalities, to allow reliable detection of these conditions and to provide useful information to avoid brain damage [22]. Transcranial Doppler ultrasound (TCD) is a non-invasive tool for measuring cerebral hemodynamic changes in the brain. High intensity transient signals (HITS) are believed to represent microembolic or gaseous particles, which can be measured intraoperatively.

TCD is a valuable tool for monitoring the brain and evaluating essential parameters such as cerebral self-regulation, brain compliance and cerebrovascular reactivity.

The TCD probe is usually placed over the temporal area. The beam is reflected back to the probe by red blood cells that circulate in the blood vessels. In this way, the flow through the intracranial arteries, such as the middle (MCA), anterior (ACA) and posterior (PCA) cerebral arteries, can be monitored. The MCA is ideal for TCD monitoring and is the only intracranial vessel used for continuous intraoperative Doppler monitoring. TCD can serve as a tool for effectively monitoring cerebral embolic events [23]. Microemboli entering the cerebral circulation appear to be among the most common causes of stroke or neurological complications during CABG surgery. Emboli can be classified into solid and gaseous forms. Many potential sources of solid emboli have been recognized. If an atheroma is removed during aortic manipulation, large solid emboli can form. Thousands of tiny lipid emboli have been discovered in the cerebral microcirculation after CPB.

Larger solid emboli (> 200 µm) clog larger arteries, causing neurological symptoms or even strokes.

Smaller solid emboli can only clog smaller arteries and arterioles, leading to oligosymptomatic or asymptomatic disease. Possible sources of gaseous microemboli include,

for example, bubble oxygenators, venous blood reservoir, air in the venous line or poor surgical deaeration.

Microbubbles circulating in the bloodstream can obstruct blood flow in the capillary beds of numerous organs, causing tissue ischemia. Following tissue ischemia, an inflammatory cascade is activated with activation of thrombocytes, stimulation of the coagulation pathway and activation of the complement pathway, causing further obstruction of microcirculation and tissue damage [24].

Numerous studies have shown that circulating microbubbles can be harmful and be one of the causes of neurocognitive deficits after cardiac surgery [25]. Especially the microbubbles that circulate in the cerebral vessels ranging from 10 to 20 µm can destroy the blood-brain barrier. The use of a gas filter during CABG surgery has been associated with a trend towards better neurological outcomes after surgery. According to Chung *et al.* [26], a significant amount of air bubbles, ranging from a few hundred to a few thousand, enter the bloodstream and reach areas of the brain during heart surgery. For the majority, air emboli recorded by transcranial Doppler ultrasound showed a diameter of less than 100 µm. In a study of the dissolution time of these bubbles, it was observed that air bubbles smaller than 38 µm disappeared before reaching the brain and not leading to any risk of cerebral hypoxia, unlike bubbles > 38 µm [27]. Some studies have analyzed the correction between cannulation site and gas emboli formation [28]. According to Hedayati *et al.* [29], axillary cannulation is cerebroprotective during median sternotomy [29]. No significant differences between cannulation sites were found in the retrospective observational study by El Kerdany *et al.* [30].

In general, a link between the neurological effect and the size of the emboli was found only for bubbles between 101 µm and 500 µm in size. This result is consistent with previous studies that demonstrated a strong relationship between bubble size and damage caused, only for bubbles larger than 1 mm in diameter [31].

New aspect to study: correlation between air embolism and systemic inflammatory response syndrome after cardiac surgery

Gas microembolism (GME), which occurs during open heart surgery, causes postoperative cognitive decline [32]. A consequence of open heart surgery is systemic inflammatory response syndrome (SIRS). It is a complex syndrome characterized by hemodynamic instability, reduction of peripheral vascular resistance (vasoplegia), accumulation of fluids in the third space and increase of inflammatory response markers. It is necessary to know this syndrome, identify it and manage it to avoid secondary complications [33]. The use of CPB or extracorporeal circulation (ECC) is thought to be one of the possible causes of SIRS, a cause of the activation of pro-inflammatory cascades. We have already seen how gas bubbles can form during cardiac surgery.

Air bubbles that embolize in small arteries and/or capillaries can cause damage due to two mechanisms: 1. Reduction of perfusion. 2. Inflammatory response.

There is therefore a correlation between air embolism and a SIRS after cardiac surgery [34]. Demertzis *et al.* found a statistically significant association between the formation of medium-sized air bubbles and the development of SIRS [35].

Morbidity and mortality increased in SIRS patients after cardiac surgery. The prevalence of SIRS after cardiac surgery is reported at between 12% and 59% [36].

Air embolism can cause a tissue ischemic response and a systemic inflammatory response [37].

Only microbubbles 41–200 µm in diameter are likely sufficient to induce inflammatory processes without causing clinically detectable ischemia.

This association between GME and postoperative SIRS is not well described in the literature and requires further confirmatory studies. This could be the basis for generating hypotheses for future prospective studies. In any case, further analyses are underway to define possible remedies to reduce gas emboli formation during cardiac surgery and reduce the negative impact on patients [38].

Conclusions

The occurrence of cerebrovascular complications after cardiac surgery is undoubtedly an important problem, responsible for much of the peri- and postoperative mortality in this type of surgery.

Therefore, it appears of paramount importance to select from the beginning the patients most prone to this type of complication and to manage them properly intraoperatively, applying the appropriate precautions, to reduce the incidence of one of the most devastating complications of cardiovascular surgery. The correlation between SIRS and stroke after open-heart surgery needs to be better understood. SIRS represents an important complication related to cardiac surgery. Future studies may aim to understand whether there are pathogenetic mechanisms, triggered by SIRS, that may promote the formation of emboli with subsequent neurological damage.

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Disclosure

The authors report no conflict of interest.

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