Role of surgical factors in strokes after cardiac surgery

Rôle des facteurs chirurgicaux dans les accidents vasculaires cérébraux après chirurgie cardiaque

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Summary
Deficient neurological disorders after heart surgery are destructive and affect vital prognosis. They concern between 3% to 9% of patients and are related mainly to embolic episodes or brain perfusion defects. The causes of these mechanisms are numerous, but surgical procedures and cardiopulmonary bypass optimization reduce their occurrence significantly.

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MOTS CLÉS
Chirurgie cardiaque ; Circulation extracorporelle ; Accidents vasculaires cérébraux ; Évolution postopératoire

Résumé
Les désordres neurologiques déficitaires après chirurgie cardiaque sont destructeurs et affectent le pronostic vital. Ils concernent entre 3 % et 9 % des patients et sont principalement liés à des épisodes emboliques ou à des déficits de perfusion cérébrale. Les causes de ces mécanismes sont nombreuses ; cependant l’optimisation des procédures chirurgicales et de perfusion extracorporelle réduisent leur survenue de façon significative.

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Abbreviations: AF, atrial fibrillation; CPB, cardiopulmonary bypass; MRI, magnetic resonance imaging.

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Background

Postoperative strokes after cardiac surgery are devastating complications and are characterized by two types of lesion [1]: type I corresponds to focal injuries leading to neurological disorders or coma, whereas type II corresponds to more subtle neurocognitive disorders, delirium states or convulsive seizures.

The incidence of stroke after cardiac operations varies from 3% to 9% according to the type of surgery, with concomitant coronary and valvular procedures representing the highest risk [2]. About 20% of strokes identified postoperatively occur after the first two postoperative days [2] and therefore may not be related strictly to a surgical or intraoperative cause. However, their effect on postoperative morbidity is significant, especially the resultant increase in intensive care unit stay, overall hospital stay and hospitalization cost. In addition, operative mortality may increase from 4% to 19%.

There are various methods for diagnosing postoperative stroke [3]. The clinical examination includes a neurological or neuropsychological examination in a specialized structure and, less frequently, a mental state examination. Computed tomography imaging of the brain, MRI and, more recently, functional MRI, confirm the diagnosis. There are also biological methods that evaluate brain cellular injury by measuring the concentration of neuron or glial proteins, such as neuron-specific enolase [4] or the glial-derived s100 protein [5], in the circulating blood. The electroencephalogram is used less frequently, especially when monitoring surgical operations.

During a surgical procedure, three different mechanisms may provoke a postoperative stroke: a defect in brain perfusion, embolic events, and an inflammatory response that in some cases amplifies the former mechanisms. Here, we propose to review these mechanisms, apart from the very specific context of cerebral protection during aortic cross surgery or congenital cardiopathies that require very specific context of cerebral protection during aortic cross surgery or congenital cardiopathies that require specific CPB techniques (circulatory arrest in deep hypothermia with various cerebral perfusion techniques). Similarly, carotid diseases concomitant with cardiac surgery will not be discussed, as they combine two types of currently non-consensual management (simultaneous or sequential). In reality, these management strategies are often dependent on the resources available in the cardiac surgery centres.

Cerebral perfusion in cardiopulmonary bypass

Cerebral autoregulation and acid–base balance: \( \alpha \)-stat

The cerebral autoregulation phenomenon maintains a regular blood flow for arterial pressures of 50 mmHg to 150 mmHg through mechanisms of vasoconstriction and vasodilatation [6]. Autoregulation is altered in some pathological conditions such as arterial hypertension or in patients with a cerebrovascular history [7]. From a pathophysiological perspective, this can be represented by a curve, the plateau of which changes according to the pathological conditions (autoregulation threshold increases in case of arterial hypertension) or the therapeutic conditions (autoregulation threshold decreases during hypothermic CPB). Variations in arterial blood gases have a significant effect, hypocapnia being vasoconstrictive and hypercapnia being vasodilatory. When CPB is performed under hypothermia, the cooling process modifies arterial blood gases content. With the \( \alpha \)-stat technique, the rule is not to correct blood gases to the patient’s temperature, which is therefore considered as normothermic [8]. This method maintains autoregulation, unlike the pH-stat technique, which is used less frequently. As normothermia is now being used routinely, such notions are less important.

Perfusion pressure

One principle in CPB is to favour the output in relation to perfusion pressures. Few randomized prospective studies have compared the influence of low-pressure and high-pressure levels on postoperative neurological events. Gold et al. compared patients operated on under CPB with an arterial pressure of 50 mmHg to 60 mmHg with patients whose arterial pressure was maintained between 80 mmHg and 100 mmHg [9]. Increasing perfusion pressure decreased stroke incidence from 7.2% to 2.4% but this difference was not statistically significant. On the other hand, the combined cardiac and neurological complications endpoint varied significantly from 12.9% to 4.8% (\( p = 0.026 \)). This trial did not allow cerebral hypoperfusion to be connected to perfusion pressure. One of the confusion biases was the shifting of the autoregulation phenomenon in relation to the age of the patient.

Indeed, brain MRI techniques allow the detection of preoperative infracranial cerebrovascular lesions in 50% of elderly patients [8]. Moreover, even if general anaesthesia provides some brain protection, 27% to 43% of patients may experience cerebral \( \mathrm{O}_2 \) desaturation during CPB [8]. This cerebral hypoxia was also found in 15% of patients undergoing “off-pump” coronary artery bypass graft surgery and was confirmed by electroencephalogram examination [8].

Pulsatility

Pulsatility in CPB has not been precisely characterized physiologically within the microcirculation [10]. The concept that a pressure curve, whether pulsed or not, is sufficient to assess the CPB pulsatility level precisely is a popular myth [11]. In fact, generating pulsatile flow depends on the energy gradient rather than the pressure gradient [12,13]. A flow that generates a pulsed pressure above 15 mmHg to 20 mmHg is considered pulsatile, while a flow that generates a pulsated pressure below 15 mmHg is considered non-pulsatile [13]. This pulsatile component is responsible for the energy side transmission within the tissues [14]. It is not evaluated in the operating room due to the lack of easily available monitoring devices. Other methods have been suggested, such as the pulsation index [15] or the pulsatility index [16], the latter being calculated after measuring blood velocities with a transcranial Doppler of the middle cerebral artery.

Pulsatile energy should be differentiated from hydraulic energy. It represents only 10% to 15% of the hydraulic energy (output–pressure coupling) but probably corresponds to
a significant physiological component. Conventional roller pumps used in CPB provide a pulsatile flow after settings of the rotor rotation speed (pulsed mode). However, when compared with centrifugal pumps, some of which are completely non-pulsatile, roller pumps in non-pulsed mode are nonetheless capable of providing a 10 mmHg to 15 mmHg pulsed pressure [17]. The concept that a roller pump produces a pulsatile flow was described 20 years ago [18]. This is not meaningless and has to be considered when reviewing various published studies postulating the use of a priori non-pulsatile roller pumps, thus making analysis of results and discussion difficult. Oxygenators and cannulae geometry also act on pulsatility absorption [19].

Currently, there is no formal evidence that pulsatility provides clinical benefit in terms of reduced postoperative neurological complications in cardiac surgery. In a literature review published by Alghamdi and Latter [20], the sole controlled, randomized trial considered to be of any value showed that pulsatile perfusion during CPB was associated with a decrease in myocardial infarctions, mortality and major complications [21]. In this study, patients operated on at 28°C hypothermia were randomized between a non-pulsatile CPB and a pulsatile CPB, generating 15% more cerebral output. No clinical neurological difference was observed.

**Haemodilution**

Haemodilution has always been used in cardiac surgery to compensate viscosity overload related to systemic hypothermia. With routine surgery increasingly being performed under normothermia, it is mainly associated with CPB priming volume. In a retrospective study, Karkouti et al. showed that haemodilution is associated with an increased stroke risk after cardiac surgery [22]. In this study, each percentage decrease in intraoperative haematocrit under CPB was associated with a 10% increase in the odds of having a postoperative stroke. Only one prospective study has tried to compare the influence of a 27% minimal haematocrit and a 15% to 17% minimal haematocrit on the incidence of postoperative cerebral complications. The haemodilution-related adverse effects led the investigators to interrupt this trial for ethical reasons [8].

There are two fundamental factors relating to the importance of haemodilution for the management of these patients. Vascular filling, especially during anaesthesia procedure, may induce a significant reduction in haematocrit that is detrimental to the patient. Moreover, excessive postoperative bleeding (surgical haemostasis quality, active antiplatelet treatment) may worsen this haemodilution, requiring excessive vascular filling and leading to an increase in transfusional risk and postoperative stroke. Therefore, it appears essential that common sense surgical and anaesthetic procedures should be applied during cardiac surgery under CPB as well as during off-pump surgery.

**Perfusion temperature**

Systemic hypothermia has been used since the introduction of cardiac surgery and its cerebral protection benefits are well accepted. In fact, the benefit of hypothermia has not been proven, as shown by a 2004 Cochrane analysis [7], the conclusions of which do not justify in any way the extended use of moderate hypothermia in routine cardiac surgery. From a practical aspect, rewarming-related lesions may be correlated to a potential hyperthermia that exceeds the final goal. Actually, Nathan et al. demonstrated that there was less cognitive deficit 1 week and 3 months after CPB when rewarming was performed from 32°C to 34°C compared with a more complete rewarming from 32°C to 37°C [23]. The suggested hypothesis would result in an exceeded normothermia, especially on the aortic perfusion cannula outflow, the cerebral effects of which would be deleterious to the patient.

**Cerebral embolisms**

Embolic propagation of macromolecules (macroembolization) differs from that of microparticles (microembolization). Embolization of macroparticles concerns the occlusion of vessels with a diameter larger than 200 μm [24]. These occlusions are possibly related to massive air embolism, usually due to human error or a set-up default in the CPB circuit, in which the suction lines are assembled incorrectly and fill the systemic circulation with air instead of purging it [25]. A systematic check of the CPB procedure is therefore mandatory. These occlusions can also be caused by embolism of particles or thrombi detached from aortic plaques during aortic operative manipulation. All these mechanisms lead to the formation of focal lesions with clinical deficit.

By comparison, microembolization concerns the occlusion of small vessels, arterioles and capillaries with an infraclinical neurological manifestation, and must be detected by specialized neuropsychological tests allowing affirmation of neurocognitive deficit or decline. These lesions occur more frequently; according to Roach et al. [1] they concern over 50% of patients when detected systematically, whereas macroembolization phenomena concern about 10 times fewer patients. Microemboli result from air microbubbles related to cardiac cavities de-airing, to circulating lipid particles or platelets aggregates, and to numerous particles associated with the surgical procedure (e.g., glove talcum powder) or originating from the CPB circuit itself.

**Aortic atherosclerosis**

Aortic atheroma severity has been correlated to postoperative strokes as well as extended hospital stay after coronary artery bypass grafting [26]. Atherosclerosis severity can be evaluated by transoesophageal echocardiography and numerous classifications have been suggested, most of them based on a progressive graduation of an intimal then parietal thickening, until the existence of mobile elements. Distribution and severity of these atherosclerotic lesions have been studied over different segments of the thoracic aorta, from the ascending aorta to the descending aorta via the aortic arch that represents the higher risk area from which supra-aortic vessels originate [26].

Anatomopathological studies have revealed that the ascending aorta is the thoracic aorta segment least affected
by atherosclerosis [27]. Search for emboli by transcranial Doppler can complete this ultrasonographical evaluation, using a temporal bone window to register ultrasonic signals on the middle cerebral artery. The lack of correlation between the frequency of these emboli observed by transcranial Doppler and the severity of the aortic atherosclerosis suggests that many emboli may be of a non-atheromatous origin [26]. Transoesophageal echocardiography is used frequently in the operating room, even routinely in some groups. Its drawback lies in poor visualization of the ascending aorta distal portion due to the shadow cone generated by the left main bronchus. This area is precisely where the surgeon has to introduce the arterial perfusion cannula. About 30% of the atheromatous plaques are unnoticed at surgical palpation [8]; more precisely, those that are non-calcified and more emboligenous. Consequently, some surgical teams prefer to use epi-aortic echocardiography, which is more sensible than transoesophageal echocardiography [7]. Nevertheless, this epi-aortic technique has limited use, probably because the handlings over the operative field can expose the patient to an additional septic risk.

**Off-pump surgery**

By the end of the 1990s, the use of off-pump surgery had increased considerably. One of its aims was to avoid inflammatory haemodynamic and microembolic disturbances. Many non-randomized observational studies demonstrated encouraging postoperative courses from a neurological aspect after off-pump surgery, with a lower incidence of postoperative stroke [28]. Most of the time, these studies compared conventional CPB techniques, unoptimized compared with off-pump surgery, the optimization of which involved many surgical factors (reduced haemodilution, maintained ventilator support, need for superior surgical haemostasis, normothermia, etc.). This explains why randomized studies have contributed less because confusion factors were better controlled [29]. Two prospective studies concluded that there was no difference between off-pump surgery and on-pump surgery in terms of postoperative stroke [30,31], as did a meta-analysis [32]. However, patients included in these studies generally presented with a low neurological risk, and embolization phenomena are possible with aortic procedures related to ascending aorta proximal anastomoses during aortoconorony bypasses. Furthermore, heart luxation, especially in case of side and inferior walls revascularization, may alter the patient’s haemodynamics [7] and necessitate vascular filling that contributes to the aggravation of haemodilution. These operative variables are likely to account for the lack of general benefit for off-pump surgery compared with on-pump CPB performed in an optimized and appropriate way, as far as the incidence of postoperative neurological complications is concerned.

**Arterial filter and cannula**

An arterial filter is included systematically in the CPB circuit, downstream of the oxygenator, and represents the last protective barrier before brain perfusion. This filter is always used because of the lawsuit implications its absence would have in the event of postoperative stroke. The filter presents a drawback by requiring an additional 300 mL filling to add to the CPB circuit priming, which also occurs in the peroperative haemodilution level. More recently, aortic cannulae combined with a filter that unfolds like a butterfly net have been proposed to surgical teams, the aim being to unfold the filter prior to aortic declamping, which is a critical moment in terms of micro- and macroparticle embolization. An international multicentre register has underlined the reduction in neurological complications in patients undergoing combined myocardial revascularization and open-heart surgery [33]. However, these cannulae have the drawback of being cumbersome, as well as not knowing before surgery if their use will be required, and the consideration of their extra cost. In the presence of a severely atherosclerosed ascending aorta with an increased embolic risk, other sites of arterial cannulation should be considered. The axillary artery provides an anterograde perfusion to the brain as well as to the organism, which is not the case via the femoral artery access that ensures retrograde perfusion, submitting the brain to embolic migrations from the ascending and horizontal aorta. During aortic dissection surgery, this axillary access has proven its superiority compared with a femoral access in preventing neurological complications when an ascending aorta cannulation is not foreseen [34].

**Various interventions on the cardiopulmonary bypass circuit**

Taylor et al. demonstrated with transcranial Doppler measurements that cerebral microembolization events during CPB increased with perfusionists’ interventions and handleings on the circuit [35]. The injection of various drugs (especially antibiotics) and the many blood samplings related to CPB monitoring initiate a microemboli incidence that is much higher than that initiated by the various CPB set-up handleings and monitoring by the surgeon. This should help in understanding why previous studies concluded on the non-atheromatous nature of microemboli [26]. This is an interesting finding, because by modifying operating room practices, it would be possible to reduce this intraoperative microembolic strain.

**Surgical suctions monitoring**

Several anatomopathological studies carried out in dogs have underlined the importance of lipid microembolization in cerebral microcirculation [36]. The use of various types of arterial filter modulates this lipid microembolization. It is especially interesting to note that the use of devices for blood scavenging and washing (Cell Saver) also reduces this microembolization significantly. This fully justifies modifying surgical behaviours to replace traditional CPB suctions with a Cell Saver, the purpose of which, after blood treatment and washing, is to transfuse only erythrocytes without the various inflammatory mediators, microparticles and other leucoplatelet aggregates. In a prospective, multicentre, randomized trial, a continuous-flow Cell Saver was associated with reduced cognitive decline in elderly patients after coronary artery bypass [37].

Obviously, these techniques still require strict respect of surgical haemostasis, to avoid exceeding the theoreti-
ical capacities of such a procedure, which could lead to platelet depletion and coagulation factors detrimental to the patient. It has also been shown that cerebral cellular injury, assessed by measurement of the s100β circulating concentration, was reduced significantly when using a Cell Saver, thus avoiding retransfusion through CPB conventional suction degradation products and inflammatory mediators present in the pericardial cavity [38]. It is essential to consider this surgical practice when analysing the scientific literature, as it has been shown clearly that the fat tissue near the pericardial cavity releases this protein ubiquitously, and it may be considered as evidence of cerebral cellular injury [39].

De-airing, CO₂ insufflation
Open-heart surgery requires de-airing of cardiac cavities prior to aortic unclamping to limit air emboli. As CO₂ is more diffusible than air, a proposal was made to insufflate CO₂ into the surgical field, to limit microembolization phenomena. In 2004, the first prospective, randomized trial in 20 patients was published and did not reveal any clinical neurological difference between two groups of patients, despite a significant decrease in the number of microemboli within the left cardiac cavities and ascending aorta [40]. Obviously, this study was too under-powered for conclusions to be drawn. Another randomized clinical trial on 80 patients showed a reduced incidence of auditory-evoked potentials but without any other significant clinical neurological effect [41]. A recent review of the literature did not prove the efficacy of this method in reducing cerebrovascular complications after open-heart surgery [42].

Inflammatory syndrome and neurocognitive decline
In 1993, Harris et al. published a paper in The Lancet reporting on pre- and postoperative cerebral MRI leading to suspected inflammatory swelling of the cerebral tissues after coronary artery bypasses [43]. Systemic inflammatory response is important after cardiac surgery under CPB. Therefore, it could be considered as a third pathophysiological mechanism explaining neurological postoperative complications. The activation of the plasmatic complement cascade is an inflammatory phenomenon observed early during surgery. The presence of glial receptors for the complement C5a fragment [44] could justify studying the effect of this inflammatory response reduction during patients' neurological follow-up. Using heparin-coated extracorporeal circuits known to reduce inflammatory response, it has been proven that reduction of complement activation correlated with a decrease in s100β protein release and executive disorders [45]. Patients benefited from procedures reducing both inflammatory response and brain cell injury at an infrastructural level and did not suffer any significant cognitive decline. These results confirm those of Heyer et al. [46]. These postoperative neurocognitive complications are usually transient, as much as inflammatory biological events after surgery under CPB can be.

Many other studies on neuropsychological complications have been carried out. Several evaluated perfusion temper-

ature and the incidence of cognitive decline. Usually this clinical research is relatively difficult to implement, requiring the collaboration of trained neuropsychologists to limit measurement bias [47].

AF is one of the various complications after cardiac surgery. The inflammatory nature of AF has been demonstrated in this surgical context. It corresponds to a second complement activation phase involving C-reactive protein during the postoperative period. The first phase results from the interaction of blood with the extracorporeal circuit surfaces [48]. It concerns the classical complement pathway (C4b) and is related to the heparin—protamine interaction at the end of CPB [49]. Reduction of this activation pathway by using heparin-coated CPB circuits reduces this inflammatory factor [50]. Using this type of circuit reduces postoperative AF events through a mechanism that is still unclear, considering the time that elapses between AF occurrence and surgery [51]. However, although these circuits reduce postoperative AF incidence associated with thromboembolization, they have not yet proven their efficacy in reducing stroke [52].

Impact of evidence-based medicine
There are numerous surgical factors involved in the incidence of postoperative stroke. Actions that take most of these factors into account could reduce stroke risk significantly. A study based upon evidence-based medicine data showed that a prevention and optimized surgical management programme led to a decrease in neurological complications (from 6.7% to 2.7%; p < 0.01) after any surgery under CPB, with reduced postoperative mortality as a consequence (from 3.8% to 2.0%; p < 0.01) [53].

Conclusion
Postoperative neurological complications, especially with a deficit, are particularly destructive. Generally, they are the consequence of macroparticle emboli related to aortic atherosclerosis. One paradox is that off-pump surgery has allowed a better understanding of the many pathophysiological processes that might induce postoperative complications, most especially neurological ones. The benefits provided by modified surgical practices and CPB are now measurable. However, our patients’ profiles have changed considerably over the past years, particularly with patients aging and increased comorbidities, which may account for delayed occurrence of postoperative stroke. Modification of current cardiological therapies, with an increased use of antiplatelet agents and preoperative interventional procedures, may alter the surgical scene. Consequently, many pathophysiological aspects will require further study as literature analysis does not offer concepts in line with patients currently assigned to surgical teams.

Conflict of interest statement
Conferences: the author has received invitations to be a contributor for Medtronic.
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