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Cerebrovascular Disease and Stroke (S Silverman, Section Editor)

Update in the Evaluation and Management of Perioperative Stroke

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Abstract

Purpose of review This review will review the current knowledge and gaps in the literature on the relationship between surgery and ischemic stroke.
Findings Surgery and ischemic stroke are interrelated phenomena as surgery is an independent risk factor for stroke and perioperative stroke increases morbidity and mortality leading to poor outcomes after surgery. This relationship and the risk of adverse outcome apply not only the clinically apparent stroke in the perioperative period but also clinically silent brain infarction detected only on radiological studies. The risk of perioperative stroke depends on several factors including (i) patient-related factors (age, history of prior stroke, and other comorbidities), (ii) procedure-related factors (type of surgery/procedure, use of cardiopulmonary bypass, antiplatelet/antithrombotic interruption, and metabolic derangement), and (iii) perioperative atrial fibrillation.
Summary With observation and retrospective data, the literature is limited to prevention and management of perioperative stroke.

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Introduction

Ischemic stroke is an episode of neurological dysfunction caused by focal cerebral, spinal, or retinal infarction [1]. Stroke is the second leading cause of death globally. In the USA, approximately 795,000 strokes occur each year [2]. Stroke costs the USA an estimated $34 billion each year including the cost of healthcare services, medications, and missed days of work. Survivors of stroke are often left with residual physical and cognitive disability. Consequences of residual disabilities lead to loss of productivity and increased healthcare costs. It has been estimated by the American Heart Association (AHA) that by 2030, annual costs of stroke will top $240.67 billion, representing an increase of 129% from current levels [3].

Perioperative stroke is a brain infarction of ischemic or hemorrhagic etiology that occurs during surgery or within 30 days after surgery [4]. Perioperative stroke increases the mortality and morbidity after surgery [5–7]. In a study of patients undergoing coronary artery bypass graft surgery (CABG), postoperative stroke resulted in longer length of stay by 5.4 days and $ 14,349 more in consumption of hospital resources [8]. In another analysis of patients undergoing carotid endarterectomy, 30-day perioperative stroke rate was 2.15% and 30-day mortality was estimated to be 17% [9]. The reported incidence varies depending on the type of surgery; risk with cardiac surgery can be up to 10% while non-cardiac, non-carotid surgeries may carry less than 3% risk. However, the true incidence is likely underestimated due to risk of misattribution of postoperative symptoms, transient nature of symptoms, or underutilization of brain imaging [10•].

The landscape of stroke management has changed since the success of endovascular thrombectomy trials and their adoption as part of the standard of care for acute ischemic stroke [11••]. Many patients with acute ischemic stroke caused by occlusion of a proximal anterior circulation intracranial artery may be eligible for hyperacute treatments and may sustain good or excellent functional outcome. More tools such as CT perfusion and MR perfusion enhance the ability to diagnose and institute rapid therapy for acute ischemic stroke. More recently, the 2018 AHA guidelines updated recommendations to support consideration of the use of intravenous thrombolytic therapy in selected patients with recent major (extracranial/-spinal) surgery where the neurologic benefit may outweigh surgical-site hemorrhage risks [12••].

Risk factors

Risk factors include both patient-related risk factors and procedure-related factors (see Table 1). Among patient-related risks, advancing age, prior history of stroke, chronic kidney disease, recent myocardial infarction, and atrial fibrillation are the most common [6, 7, 19]. In a cohort of patients undergoing cardiac surgery, prior history of stroke, previous cardiac surgery, hypertension, diabetes mellitus, peripheral vascular disease, prolonged cardiopulmonary bypass, high transfusion requirement, and urgent (non-elective) surgery were all independent predictors of stroke [20]. For non-cardiac surgery, history of prior stroke, need for repeat surgery, and postoperative myocardial infarction were some of the risk factors associated with perioperative stroke. Most of these patients share similar risk factors for thrombotic stroke such as hypertension, nicotine use, diabetes mellitus, and hyperlipidemia [21]. In addition to the traditional risk factors, patients with patent foramen ovale (PFO) undergoing non-cardiac surgery were also found to have a 2.66-fold elevated risk of ischemic strokes [22].

Table 1. Risk factors for perioperative stroke [7, 13–18]

A. Patient related	
Risk factor	**Adjusted odds ratio (95% CI)**
Age > 62	3.9 (3–5)
History of TIA	1.9 (1.3–2.6)
History of Stroke	2.9 (2.3–5.8)
Myocardial infarction in the last 6 months	3.8 (2.4–3.4)
Dialysis dependency	2.3 (1.6–3.4)
Hypertension	2 (1.6–2.6)
B. Surgery related	
Type of surgery	**Risk (%)**
CABG	1.5–5.2
CEA	2.15
Mitral valve replacement	2.1
Aortic valve repair	1.7–2.5
Orthopedic surgery	0.2–0.9
Non-carotid vascular surgery	0.5–0.8
Head and neck surgery	0.2–5

Perioperative atrial fibrillation

The risk of perioperative atrial fibrillation (POAF) in cardiac surgery varies between 30 and 50%, where CABG is lowest in the spectrum (~ 30%), followed by valve surgery (~ 40%), and highest with the combination of CABG and valve surgery (~ 50%) [23•, 24•, 25•]. For non-cardiac surgery, the risk of POAF is noted to be 0.4 to 26% depending on the type of surgery and other factors [26–28]. The wide range of POAF risk for a single type of surgery is attributed to the variation in the definition of POAF, duration of monitoring, method of monitoring, and the type and methodology of study evaluating the risk. Patients with new-onset atrial fibrillation in the perioperative setting had 37% increased risk of long-term stroke [29].

Asymptomatic carotid stenosis

During cardiac surgery in patients with underlying carotid disease, the perioperative stroke rate ranges from 1 to 16%. The risk correlates with the degree of stenosis and the risk is highest in patients with a prior history of stroke [13, 30–33].

With CABG, perioperative stroke risk is 3% in patients with asymptomatic unilateral moderate to severe stenosis, 5% in those with bilateral stenoses, and 7–11% in patients with carotid occlusion. Interestingly, more than half of

territorial infarctions on CT scan/autopsy did not correspond to the carotid disease alone [30]. This supports the observation of atheroembolism (e.g., aortic arch) or cardioembolism as prominent perioperative risk factors for stroke in CABG [34]. It is a matter of debate whether carotid stenosis should be treated before CABG or not because carotid procedures themselves introduce an additional risk of perioperative stroke.

Procedure-related risks

Carotid endarterectomy (CEA) and carotid artery stenting (CAS) are two options for treating carotid artery stenosis and reduce the long-term risk of stroke. The Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST) reported that the risk of perioperative stroke was 4.1% with CAS and 2.3% with CEA [33]. The risk of ischemic stroke has overall decreased with carotid stenting with the use of embolic protection device and the overall risk is estimated to be lower than 2% [35].

CABG and percutaneous coronary intervention (PCI) are performed for coronary revascularization in patients with left main and multivessel coronary artery disease. Stroke is the most feared complication of coronary revascularization with 30-day rates of 0.4% with PCI and 1.1% with CABG in a patient-level pooled analysis from 11 clinical trials published in 2018. Overall stroke risk ranges from 1.4 to 3.8 with CABG [36]. In a meta-analysis of 3 trials, comparing the patients who underwent CABG on or off cardiopulmonary pump, there was no difference in rates of stroke, MI, and death among the 2 groups at 5-year follow-up [37–39]. Similar results were also noted in 5-year follow-up [40].

Transcatheter aortic valve replacement (TAVR) for high surgical risk patients with severe aortic stenosis (and an option for intermediate-risk patients) represents significant progress in surgical options for patients with structural heart disease but continues to harbor risk of perioperative stroke [41–47]. The incidence of clinically silent cerebral ischemic lesions on post-procedure MRI ranges from 68 to 86%, compared with 47% for open surgery [41, 48]. Recent studies and case reports have shown a decrease in ischemic stroke risk that can be attributed to improved skills, advanced techniques and devices, and use of embolic protection devices [42]. In a long-term follow-up of the Placement of Aortic Transcatheter Valves (PARTNER-I) trial, patient population risk of stroke in 30 days was estimated to be 3.8% [43]. Both transfemoral and trans-apical approaches carry about the same risk of stroke [44].

Pathogenesis

Several mechanisms account for the occurrence of stroke after surgery. In cardiac surgery, embolism may originate from intracardiac thrombi, aortic arch atheroma, or perioperative atrial fibrillation. The majority of the strokes in the perioperative period are ischemic in nature; hemorrhagic strokes are comparatively rare [49]. Thrombosis appears to be responsible for a majority of strokes in non-cardiac surgery. There is an elevation in pro-inflammatory cytokines and evidence of endothelial dysfunction after surgery leading to progression of atherosclerosis and thrombosis [50].

The mechanisms of stroke during CABG are embolic phenomenon, new-onset atrial fibrillation, and hypotension during and after the procedure in patients with extracranial and intracranial atherosclerotic disease. Hypotension during the surgery precipitates cerebral hypoperfusion and infarction of the brain tissue.

Early peri-procedural strokes after structural heart interventions are mainly related to embolization from particulate matter during device and catheter manipulation across calcified valves, balloon pre- and post-dilatation, valve dislodgement, and air embolism. There is evidence of heterogeneous material (thrombus, fibrin, tissue fragments from valve leaflets, and calcified material) captured in embolic protection devices during TAVR [45]. Subacute strokes are likely related to new-onset atrial fibrillation, the incidence of which is higher in trans-apical approach.

Management

Limited data is available in the form of observational and retrospective studies to guide management in the prevention and management of postoperative strokes.

Preoperative measures to decrease the risk

Careful surgical planning including choice of procedure, timing of procedure, and duration of antiplatelets or anticoagulation hold is the first step in minimizing the risk of stroke perioperatively.

The role of carotid stenosis

Carotid artery ultrasonography is reasonable in selected patients deemed high risk (> 65 year of age, coronary artery disease, peripheral arterial disease, history of TIA or stroke, hypertension, smoking, and DM) [51•]. In patients with a previous history of stroke or TIA and moderate to severe carotid stenosis (50–99%), it may be reasonable to consider carotid revascularization in conjunction with CABG [51•]. However, various approaches are taken in patients with concomitant existence of significant carotid stenosis and coronary artery disease, such as staged versus combined surgery. No significant mortality and morbidity difference have been reported among the various approaches. The overall complication rate after combined revascularization of the coronary and carotid artery of approximately 9% is still considerably high [52]. Additionally, CABACS (Coronary Artery Bypass Graft Surgery in Patients with Asymptomatic Carotid Stenosis) compared synchronous CEA of asymptomatic high-grade carotid artery stenosis versus no carotid operation in patients undergoing CABG surgery. The trial was stopped early due to slow recruitment; hence, there was no evidence for a treatment-grouped effect. In that limited data, the patients who underwent synchronous CABG and CEA had twice the rates of stroke or death at 30 days and 1 year compared with isolated CABG [53]. More recently carotid artery stenting prior to CABG has shown superiority in small series [54•]. It remains questionable whether the observed risk of combined (simultaneous) surgery in asymptomatic patients with high-grade carotid stenosis is justified at all. The evidence of an advantage of combined surgeries in asymptomatic

carotid stenosis and symptomatic coronary artery disease is still pending. Indeed the role of intervention for asymptomatic carotid disease has been called into question, particularly in the era of contemporary aggressive medical pharmacotherapy. The currently enrolling trial CREST 2 (Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Trial) is a randomized controlled study of carotid revascularization and intensive medical management versus medical management alone in patients with asymptomatic high-grade carotid stenosis.

Deciding the timing of surgery

Following a stroke, cerebrovascular reserve takes a few weeks to months to return to baseline. During this time, the dysfunctional cerebral autoregulation is believed to make the brain susceptible to secondary neuronal injury. Based on the data from a large observational study which revealed that major cardiovascular events plateaued at 9 months following ischemic stroke, the American College of Surgeons recommended deferring elective surgery for at least 9 months after ischemic stroke [55•, 56]. Data from the Danish National Patient Registry also showed that adverse cardiovascular outcomes and mortality were increased among patients with recent stroke [57]. However, these events were higher 4 to 14 days after stroke compared with 1 to 3 days after stroke. It was hypothesized that cerebral autoregulation does not get compromised until about 4 days post-primary ischemic insult. The strength of these data is limited by potential bias associated with a retrospective nature of the study and no information on the etiology of the stroke and medication.

Antithrombotic management

Patients undergoing surgery are frequently prescribed antithrombotic pharmacotherapy that interferes with hemostatic pathways. Assessing the bleeding risk can be quite challenging and different surgical procedures have different bleeding risks. An important consideration is whether to interrupt antithrombotic or anticoagulant therapy and if so, for how long. The time required to regain normal platelet activity depends on multiple factors, including the pharmacokinetics of the drug and patient risk factors. Bleeding in vital organs such as the brain or spinal cord can lead to adverse outcomes. Certain organs such as the spleen, liver, and kidney have a higher risk of bleeding because of increased vascularity. Holding antithrombotic agents for procedures is associated with reduced perioperative bleeding and need for transfusion which in turn decreases the mortality. However, during this period of interrupted antithrombotic therapy, patients are exposed to increased risk of thrombotic events. Since there is a paucity of robust evidence on bleeding risk stratification, every effort should be made to obtain bleeding risk assessment from the operating surgeon based on type of surgery and patient's individual risk factors.

Antiplatelet therapy

Guidelines published by various societies recommend stopping antiplatelets before a planned major non-cardiac surgery. The American College of Thoracic Surgeons recommends discontinuing P2Y12 inhibitors for a few days prior to

cardiovascular surgeries [58]. Similar consensus exists for neurosurgical procedures and spine procedures [59]. For minor procedures or procedures in which the perioperative bleeding risk is felt lower than the thromboembolic risk of stopping antithrombotic therapy (e.g., patient with recent ischemic stroke), these therapies may be continued.

Bleeding risk is minimal for certain minimally invasive procedures such as dental extraction, cataract surgeries, and diagnostic endoscopies [60–62]. These procedures do not require discontinuation of antithrombotic agents. In the case of dental producers, bleeding can be controlled with local measures such as mechanical pressure, tranexamic mouthwash, mechanical pressure, and surgical suturing.

Anticoagulation

The HAS-BLED score (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile INR, Elderly, Drugs/alcohol concomitantly) was developed to predicate major bleeding in anticoagulated patients with nonvalvular atrial fibrillation. In an observational registry, scores of > 3 predicted higher bleeding risks in patients undergoing invasive cardiac procedures [63]. Guidelines from ACCP recommend interrupting warfarin 5 days before surgery [64]. Conditions with a high risk of thromboembolism such as recent DVT and mechanical heart valves require bridging with heparin to minimize the thromboembolic events in the perioperative period. The American College of Surgeons recommends starting IV heparin bridge when INR becomes sub-therapeutic and continuing until 24 h prior to the procedure [56]. For surgeries with high bleeding risk, warfarin is to be resumed 12–24 h after the surgery. Heparin should be discontinued once the INR reaches therapeutic level.

The BRIDGE trial tested whether bridging was essential in patients with atrial fibrillation on warfarin undergoing non-cardiac surgeries [65••]. The incidence of arterial thromboembolism was 0.4% in the no-bridging group and 0.3% in the bridging group. Major bleeding was lower (1.3% vs. 3.2%) in the no-bridging group compared with the bridging group. The caveats were mean low $CHADS_2$ score of 2.3 and 89% of the procedures were deemed minor. The applicability of these results to patients with higher thromboembolic risks as well as patients on direct oral anticoagulants is uncertain.

Intraoperative measures to decrease the risk

Management of intraoperative hypotension is a modifiable risk factor to minimize the risk of perioperative stroke [66]. Mean arterial pressure (MAP) of below 65 mmHg for longer than 10 min is associated with increased incidence of stroke [67•]. Another study defined intraoperative hypotension as reduction in MAP of 30% from baseline, showing increased risk of stroke. Maintenance of MAP above these numbers may help prevent hypoperfusion-related ischemic injury. Use of embolic protection device during the percutaneous structural intervention has shown a decreased in the incidence of intraoperative stroke [68]. Intraoperative monitoring in the form of intraoperative electroencephalogram and transcranial Doppler ultrasound has value in early detection of cerebral hypoperfusion and embolism [69].

Role of oral anticoagulation in perioperative atrial fibrillation

The use oral anticoagulants (OAC) in POAF are an emerging area. The ACC/AHA/HRS 2014 atrial fibrillation (AF) guidelines provide class IIa support for the use of OAC in POAF in cardiac surgery patients who are at high risk for stroke [70]. These guidelines specifically do not comment on OAC in POAF in non-cardiac surgery patients, but a similar risk of stroke in patients with POAF in non-cardiac surgery was reduced with the use of OAC [26]. These have been supported by 2016 European Guidelines as well [71]. An area of uncertainty is the minimum time spent in AF in the postoperative period required to increase risk of development of stroke and warrant primary prevention with the use of OAC [71•, 72, 73•]. Presently, a balancing act with the absolute risk of stroke development, its relative risk on OAC, and bleeding risk on OAC (using scoring system like HAS-BLED) should be assessed and shared decision-making with the patient should be undertaken.

Acute management of acute ischemic event in perioperative setting

According to earlier iterations of the AHA/ASA Guidelines for management of acute ischemic stroke, surgery within the last 2 weeks of symptom onset was a relative contraindication to IV thrombolysis [74]. This has been modified recently where careful risk and benefit discussion should be made between the teams and if benefit is higher than risk of bleeding, IV thrombolysis can be performed [12].

Mechanical thrombectomy has helped achieve further success in acute ischemic stroke management [11], both for patients ineligible for IV thrombolysis as well as for patients who receive IV thrombolysis but harbor acute intracranial large-vessel occlusion amenable to treatment. The window for mechanical thrombectomy further expanded with the more recent acute treatment trial successes [75••, 76]. These results distilled in 2018 AHA/ASA Guidelines make provisions for performing endovascular thrombectomy up to 24 h since last known well if there is imaging evidence of salvageable brain tissue and large-vessel occlusion [12, 75••, 76••]. Because it carries a lower systemic and surgical-site bleeding risk, endovascular mechanical thrombectomy provides access to acute stroke therapy previously unavailable to many perioperative stroke patients.

Inpatient acute ischemic stroke management had been very challenging because of the difficulty in identifying neurological symptoms immediately in postoperative patients. More frequent neurologic clinical bedside assessments help in identifying neurological change within the window for intervention. Patients on a mechanical ventilator should be examined off sedation for better assessment. Each patient with acute onset neurological symptoms perioperatively should be considered a potential candidate both for IV thrombolysis and endovascular thrombectomy in the presence of large-vessel occlusion fulfilling the severity/disability criteria.

Measures for secondary stroke prevention

After the acute management is provided, the next task is the secondary prevention for stroke. Patients should receive antiplatelet therapy as soon as possible. In patients with indication for anticoagulation, anticoagulation is held post-stroke for a short duration because of the high risk of hemorrhagic conversion

in the infarcted brain tissue. This duration depends on the size of the stroke and range from 2 days to 2 weeks and is highly variable in clinical practice. In patients with atrial fibrillation and contraindication to anticoagulation because of high bleeding risk, left atrial appendage septal occluding device can be considered [77•, 78]. A few clinically encountered examples of such situations are hemorrhagic metastasis to the brain, cerebral amyloid angiopathy, and severe GI bleeding with anticoagulation.

Conclusion

Stroke is a known and feared complication of many surgeries, particularly cardiac and vascular surgeries. A multidirectional approach to minimize the risk of stroke may help minimize these outcomes. Minimal interruption in the preventative therapy and avoidance of hypotension perioperatively can help achieve better outcomes in high-risk patients. Postoperative patients can be candidates for IV thrombolysis and endovascular thrombectomy in acute stroke. Activation of the stroke team should be performed when a change in neurological examination is suspected. Additional research is needed to understand the pathophysiological mechanisms of postoperative strokes and strategies to minimize neuronal injury.

Compliance with Ethical Standards

Conflict of Interest
The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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