Review

Understanding noncardiac complications following coronary artery bypass graft surgery

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Practice Points

Bleeding
- Blood transfusion is associated with worse short- and long-term outcomes following cardiac surgery.
- The use of antifibrinolytic agents is associated with reduced bleeding.

Heparin-induced thrombocytopenia
- This develops in 2% patients on cardiopulmonary bypass.
- Treatment involves stopping heparin immediately and changing to a non-heparin anticoagulant.

Deep sternal wound infection
- Insulin-requiring diabetes, obesity, chronic airway disease and the use of bilateral internal thoracic artery are risk factors for deep sternal wound infection.
- Prophylactic antibiotics, nasal passage decolonization and tight perioperative blood sugar control are important measures for reducing the risk of deep sternal wound infection.
- Vacuum-assisted closure therapy has become the preferred choice for the initial management of deep sternal wound infection.

Renal injury
- Renal failure requiring dialysis is associated with high mortality.
- Adequate hydration, maintaining adequate blood pressure on-pump and avoidance of nephrotoxins are important preventative measures.

Cerebral injury
- Stroke is one of the most devastating complications of coronary artery bypass grafting.
- Microemboli on-pump are associated with a high risk of stroke.
- Avoidance of aortic manipulation may be able to reduce the risk of stroke.

Pulmonary injury
- Acute respiratory distress syndrome represents the most extreme form of lung injury, which may be provoked by an inflammatory response to the cardiopulmonary bypass circuit.

Intra-abdominal injury
- Gastrointestinal complications are rare, but associated with high mortality.
- A high index of clinical suspicion is critical to make an early diagnosis.

Coronary artery bypass grafting (CABG) remains the most widely performed cardiac operation in the western world. Over recent decades, remarkable technical progress has been made allowing the operation to be performed with low morbidity and mortality. The large majority of CABGs are still carried out on pump utilizing the heart–lung machine. In this Review, the noncardiac complications of CABG are discussed including etiology, pathophysiology, treatment and prevention.

Keywords: bleeding • cardiopulmonary bypass • cerebral injury • complications • coronary artery bypass grafting • pulmonary injury • renal injury • sternal wound infection

Future Medicine part of fsg

Coronary artery bypass grafting (CABG) remains the most commonly performed cardiac operation in the western world. In the UK and Ireland, isolated CABGs accounted for 58.3% of all cardiac operations in 2008. Mortality has declined from 2.3 to 1.5%, between 2001 and 2008 [1]. According to the Australian and New Zealand Society of Cardiac and Thoracic Surgeons (ANZSCTS) database, approximately 13,000 isolated CABGs are performed annually in Australia, with a decrease in mortality for elective procedures from 1.2 to 0.6% in Victoria alone between the period of 2001 and 2006 [2]. Despite the improved outcomes, CABG still has potential for significant morbidities. The majority of CABGs are still carried out 'on-pump' with the help of the heart–lung machine. A significant proportion of CABG-related complications may be attributed to the use of cardiopulmonary bypass (CPB). While vast improvements have been made with the extracorporeal apparatus, surgical techniques and perioperative patient care, many adverse effects continue to complicate cardiac surgery using CPB. The purpose of this Review is to provide a general summary of the important noncardiac complications following CABG. Where relevant, off-pump CABG is discussed in relation to individual complications. However, we do not intend to compare the two surgical techniques here.

Bleeding

Bleeding remains a common complication after CABG. Patients undergoing CABG often need transfusion support, and occasionally re-exploration for excessive bleeding. Most patients who bleed excessively in the early postoperative period have incomplete surgical hemostasis. However, some other patients bleed diffusely from various hemostatic disorders. Acquired transient defects in platelet function or number are the primary contributor to abnormal hemostasis. Less common causes include vitamin K-dependent clotting factor deficiencies, fibrinolysis and heparin rebound [3].

During the initial postoperative phase, assessment for patients' risk of bleeding and coagulation profile is carried out simultaneously. Chest tube drainage volume and patency should also be frequently monitored, alongside other supportive measures including maintenance of normothermia and adequate control of blood pressure. Re-exploration is recommended if bleeding exceeds 400 ml for 1 h, >300 ml/h for 2–3 h, or >200 ml/h for 4 h, regardless of the coagulation profile results.

Platelets can be used in the following settings: excessive bleeding with thrombocytopenia (<50 × 10^9/l) or platelet dysfunction (e.g., CPB, preoperative antiplatelet agents). Cryoprecipitate is indicated for either hypofibrinogenemia (<80 mg/dl) or congenital dysfibrinogenemia. The American Society of Anesthesiologists (ASA) guidelines recommend transfusion of fresh frozen plasma in cases of excessive bleeding with abnormal coagulation profile (prothrombin time [PT] >1.5× normal, activated partial thromboplastin time [APTT] >2.0× normal), isolated coagulation factor deficiencies for which specific factor concentrates are unavailable, or for urgent reversal of warfarin therapy [4].

The ASA panel recommends that packed red blood cells (pRBCs) be used when hemoglobin (Hb) level falls below 6 g/dl; signs of organ ischemia and active bleeding. When Hb level is between 6 and 10 g/dl, the need for transfusion is based on a patient's risk for complications of inadequate oxygenation. Transfusion is deemed unnecessary when Hb level >10 g/dl. Intraoperative transfusion of pRBCs is guided by the hematocrit (Hct) level [5]. An intraoperative Hct level below 21–24% is generally considered a trigger for transfusion as lower levels of Hct are associated with worse outcomes [6]. On the other hand, abundant evidence suggests that perioperative blood transfusion portends worse patient outcomes, both in the short and long term [7,8]. It is not entirely clear whether a low Hb/Hct *per se* or secondary transfusion is responsible for the worsened outcomes. However, a strong interplay does exist between major bleeding, anemia and transfusion, with the latter two amplifying the deleterious impact of major bleeding on operative outcomes [9].

Similarly, patients requiring chest re-exploration for bleeding have significantly higher morbidity, including stroke, low cardiac output, acute renal failure, sternal wound infection and prolonged mechanical ventilation; as well as mortality. In addition, more complications occur among patients who have delayed re-exploration (>12 h), reflecting the longer time of hemodynamic instability, increased blood loss and amount of blood transfusions [10].

Prevention

Postcardiac surgical bleeding can be effectively reduced with the use of antifibrinolytic agents. These include lysine analogs (ε-aminocaproic and tranexamic acid) and serine protease inhibitors (aprotinin). The lysine analogs exhibit their antifibrinolytic effect by inhibiting the activation of plasminogen to plasmin. Aprotinin interferes with the coagulation cascade and fibrinolysis through its inhibition of kallikrein and serine proteases, respectively. Despite its positive effect on coagulation, randomized trials have shown aprotinin to be associated with higher rates of myocardial infarction and death, resulting in its withdrawal from the market in 2007 [11–13]. The 2011 Society of Thoracic Surgeons (STS) and the Society of Cardiovascular

Anesthesiologists (SCA) Blood Conservation Clinical Practice Guidelines recommends the use of lysine analogs as a safer alternative in adults [14]. The use of tranexamic acid is associated with convulsive seizures, thus, it needs to be used with caution in patients with history of seizure disorders [15].

Perfusion methods that minimize bleeding and subsequent blood utilization, include modified ultrafiltration (MUF) and minicircuits [14]. MUF removes excess priming volume, thereby limiting expected hemodilution after completion of CPB. Boodhwani *et al.,* in their meta-analysis involving more than 1000 patients found greater reduction in bleeding and blood product usage with MUF, compared with conventional ultrafiltration [16]. Minicircuits reduce the priming volume required, resulting in less hemodilution and need for blood transfusion. This has been confirmed by several randomized analyses [17,18]. Similarly, a recent meta-analysis of 13 trials found significantly reduced postoperative blood loss with minicircuits [19].

The importance of meticulous surgical technique in reducing intraoperative blood loss cannot be overemphasized. The adage 'dry in dry out' highlights the importance of careful hemostasis as blood loss can lead to dilutional coagulopathy, which in turn leads to more bleeding. Dilutional coagulopathy can be minimized by the use of intra-operative blood salvage. There are two existing blood-salvaging techniques, namely direct transfusion of unprocessed circuit blood or transfusion of processed circuit blood, by either centrifugation or ultrafiltration. Based on available literature, there is no distinction between these techniques for limiting blood loss and usage of blood products [14]. A meta-analysis performed by Wang *et al.* also suggests that blood cell salvage may be beneficial only when used throughout the entire operation [20].

Off-pump coronary revascularization is another sensible strategy for blood conservation, provided no conversion to on-pump approach is performed [14]. Sellke *et al.* in their extensive review found a common trend towards reduced bleeding and the need for blood transfusion among patients treated with the off-pump approach [21].

Heparin-induced thrombocytopenia

Unfractionated heparin remains the standard anticoagulant agent used during CPB. Heparin-induced thrombocytopenia (HIT) develops in approximately 2% of patients undergoing on-pump cardiac surgery [22]. This is caused by interaction of immunoglobin-G antibodies with heparin-platelet factor 4 complex, producing platelet activation. The event usually occurs after 5–10 days of heparin exposure, but occasionally can present earlier in patients with previous heparin exposure. Fortunately, heparin-antibodies are transient and disappear within 100 days, thus permitting safe heparin rechallenge in patients with known or suspected HIT [22]. The majority of patients experience mild thrombocytopenia with no bleeding, although occasionally some may suffer from major bleeding, arterial or venous thrombotic complications.

HIT should be considered in patients with a platelet count drop of more than 50% within 5–10 days of heparin exposure, with the exclusion of other possible differentials [23]. Commercially available immunoassays for HIT are broadly classified into two types: first, functional assays for the detection of platelet-activating antibodies; and second, ELISA for the detection of platelet factor 4–heparin complexes. A negative result obtained with the immunoassays generally excludes HIT. The high sensitivity with ELISA testing, however, may give a false-positive result as it detects nonpathogenic antibodies often generated by heparin-treated patients [24].

Treatment involves stopping heparin immediately and replacing with an alternative non-heparin anticoagulant agent, such as lepirudin, argatroban or danaparoid [22]. According to several studies, risk of thrombosis in HIT patients managed by heparin cessation alone remains high, ranging from 23 to 51.6%. Routine noninvasive imaging of lower limbs is strongly recommended, as subclinical DVT is commonly reported in HIT patients [25]. Warfarin therapy should be avoided in HIT patients, as acute depletion of anticoagulant protein C along with the initial unopposed procoagulant effects of warfarin can precipitate DVT to venous limb gangrene. After platelet recovery has occurred (to at least 100 × 10^3/µl), oral anticoagulants can be commenced in modest doses together with an alternative non-heparin anticoagulant during transition [26].

Deep sternal wound infection

Risk factors

Deep sternal wound infection (DSWI) is a rare, but serious complication following median sternotomy. The overall incidence varies from 1–3% [27]. Risk factors include insulin-requiring diabetes, obesity, chronic lung disease, left ventricular dysfunction, peripheral vascular disease, reoperation and re-exploration for bleeding [27–29]. Bilateral internal thoracic artery (ITA) harvest has also been associated with DSWI. When the ITA is harvested as a pedicled conduit, a significant degree of sternal devascularisation has been observed. A skeletonized technique, which spares the internal thoracic veins and collateral blood flow to the sternum, has been shown to cause less sternal devascularisation than the pedicled technique. A large analysis by Deo *et al.* involving 126,235 diabetic patients who

underwent isolated CABG, demonstrated skeletonized bilateral ITA harvest was not associated with increased DSWI compared with single ITA harvest. In contrast, there is significant increased risk when pedicled technique was utilized in bilateral ITA harvest [30].

According to guidelines released by the Centre for Disease Control and Prevention, diagnosis of DSWI must meet one of the following criteria: first, organism cultured from mediastinal fluid or tissue; second, evidence of DSWI observed during operation or on histopathology; or third, chest pain, sternal instability or fever (>38°C) without another recognized cause, accompanied by purulent discharge from mediastinum and/or organisms cultured from blood or mediastinal drainage and/or mediastinal widening on x-ray [31] The diagnosis of DSWI by thoracic computed tomography (CT) scans appears unsatisfactory in the early postoperative period. Yamashiro *et al.* demonstrated that CT had a sensitivity of 100% for mediastinitis, but a specificity of only 39% through the early period (<21 days). For late presentations (>21 days), the specificity of CT scan is considerably better at 85%. Most common CT findings included pleural effusion, increased attenuation of mediastinal fat, pericardial effusion, mediastinal fluid collection and free gas bubbles [32].

Prevention

Several preventive strategies acting at different stages of surgery have been proposed (Box 1) [29,33,34].

According to ACCF/AHA guidelines, prophylactic antibiotic administration and strict blood sugar control are strongly recommended to reduce the risk of DSWI. A first- or second-generation cephalosporin should be delivered within 60 min of incision and discontinued within 48 h. Prophylaxis with vancomycin should be advocated based on methicillin-resistant *Staphylococcus aureus* colonization. The use of continuous insulin infusion to maintain perioperative glucose level ≤180 mg/dl is strongly recommended [29]. Maintaining tight glucose control in patients undergoing CABG surgery has been repeatedly shown to reduce the incidence of DSWI [35]. Furnary *et al.* reported the use of continuous insulin infusion aimed to maintain blood glucose levels <200 mg/dl reduced the incidence of DSWI by 66%, compared with those receiving intermittent subcutaneous insulin [36].

Nasal carriage of *S. aureus* is a well-recognized risk factor for postoperative DSWI. A recent meta-analysis by Van Rijen *et al.* showed an 80% reduction in *S. aureus* infection in carriers treated with mupirocin compared with only 30% of those treated with placebo [37]. Nasal carriage status should be identified either by conventional microbiological culture methods or by real-time polymerase chain reaction before commencing mupirocin ointment.

Treatment

Currently, the optimal treatment strategy for DSWI remains controversial. Robicsek proposed three basic principles of infection control: first, infection should be curtailed within the shortest time possible; second, adequate debridement and drainage of the infected areas; and third, sternal stability should be established [38].

The conventional forms of treatment include surgical debridement with frequent open wound dressings or closed irrigation and drainage. Open chest management has some drawbacks, namely, insufficient chest stability requiring prolonged ventilation and immobilization [28]. Continuous irrigation and drainage with primary sternal closure was later advocated, in 1963. However, reports on the results of this approach have been disappointing with high rates of failure [39].

Primary, or delayed wound closure using regional myocutaneous with or without omental flaps has been the mainstay treatment option for DSWI. However, complications such as chronic chest wall pain, hematoma or seroma requiring drainage, arm or shoulder weakness, and flap necrosis are not uncommon following myocutaneous flap reconstruction [40–42]. Milano *et al.* compared the technique employing omental and pectoral flaps for closure of sternal wound defect, and found that the length of procedure (221 vs 284 min) and hospital stay (10.7 vs 18.8 days) improved with omental flap procedure. The authors also reported improved short-term clinical outcomes in patients treated with omental flaps [41].

Vacuum-assisted closure (VAC) is the latest treatment innovation for managing DSWI. This technique promotes healing by applying negative pressure onto a wound. The negative pressure therapy appears to stimulate granulation-tissue formation, enhance localized blood flow and reduce wound exudates and bacterial colonization.[43,44]. Furthermore, VAC therapy allows patients to mobilize early while the wound heals. Several studies have reported favorable clinical improvement with VAC dressing, either as a single-line therapy or as an adjunct to definitive surgical closure. For instance, De Feo *et al.* reported lower mortality (1.4 vs 3.6%; p = 0.35) and reinfection (1.4 vs 16.9%; p = 0.001) rates, and reduced length of hospital stay (27.3 ± 9 vs 30.5 ± 3 days; p = 0.02) with VAC therapy compared with conventional treatment[45]. A recent study by Baillot *et al.* reported similar results, showing that the mortality rate dropped from 14.1 to 4.8% when VAC therapy was used [46]. Finally, Fleck *et al.* compared 132 patients with poststernotomy wound infection and observed lower

rates of sternal re-infection with VAC therapy followed by delayed primary closure or sternal reconstruction compared with immediate primary closure [47].

Renal injury

Risk factors

Despite improvement in perioperative management and surgical techniques, renal injury remains a frequent complication following cardiac surgery. Depending on the definitions used, the incidence of acute kidney injury (AKI) occurs in 1–30% of all patients, with associated mortality as high as 30% [48]. The lack of general consensus on the definition of AKI has recently led panels of experts to propose a more unifying classification. The Acute Kidney Injury Network (AKIN) and the Risk, Injury, Failure, Loss and End-stage Kidney (RIFLE) criteria characterized the severity of renal injury based on the changes in serum creatinine (sCr) and urine output (Tables 1 & 2) [49,50].

Risk factors for AKI include female gender, congestive heart failure, diabetes mellitus, preoperative use of intra-aortic balloon pump, emergency status and an elevated preoperative sCr. The preoperative sCr level is considered the strongest predictor for developing postoperative AKI in cardiac surgery patients. Approximately 10–20% of patients with a preoperative sCr of 2 to 4 mg/dl are at risk of developing AKI that requires dialysis. The risk rises to 30% in patients with a baseline sCr greater than 4 mg/dl [48]. Hemodilutional anemia has also been shown to cause renal injury by reducing tissue oxygen delivery and worsening oxidative stress. A retrospective study by Habib *et al.* found that hemodilution during CPB with a hematocrit <24% was associated with postoperative AKI requiring dialysis [51].

The causes of AKI following cardiac surgery are multifactorial. During CPB, the kidneys are exposed to alterations in flow dynamics via the loss of pulsatile blood flow, changes in pump flow rate and renal vasoconstriction, resulting in ischemia–reperfusion injury [52]. CPB-related embolization has also been implicated in the occurrence of AKI. Emboli include air, anaesthetic gas, lipids, platelet aggregates and atheromatous plaques from aortic manipulation [53]. Additionally, blood contact with artificial CPB surfaces initiates an inflammatory response with activation of the complement network, the coagulation system, and free radical and cytokine production, which may further contribute to kidney injury [48].

Box 1. Preventative measures to reduce deep sternal wound infection.

Preoperative
- Antibiotic prophylaxis (cephazolin or vancomycin)
- Antiseptic showering (chlorhexidine or povidone-iodine)
- Hair removal (with electrical clippers close to the time of surgery)
- Nasal decolonization with intranasal mupirocin

Intraoperative
- Tight blood glucose control
- Adherence to good surgical techniques (gentle tissue handling, effective hemostasis, elimination of dead space, hypothermia prevention)
- Internal thoracic artery harvesting technique (skeletonized technique)
- Wound dressing (adequate coverage of surgical wound incision, breathable antimicrobial dressing)

Postoperative
- Blood glucose control
- Postoperative incision care (aseptic technique for wound dressing change)

Novel biomarkers

It is generally accepted that the conventional renal biomarkers such as creatinine and urea have limited value in diagnosing AKI. These markers do not reflect injurious changes to the kidney in real time and require time to accumulate before reaching abnormal serum concentrations. Urine output is sensitive to changes in renal hemodynamics, but is considered less specific, except when it is significantly diminished or absent [54].

Table 1. Classification systems for acute kidney injury: The Acute Kidney Injury Network classification.

Stage	sCr criteria	Urine output criteria
1	Increased sCr ≥0.3 mg/dl or ×1.5- to 2-fold from baseline	<0.5 ml/kg/h >6 h
2	Increased sCr ×2- or 3-fold from baseline	<0.5 ml/kg/h ≥12 h
3†	Increased sCr > 4.0 mg/dl or ×3-fold from baseline with an acute increase of at least 0.5 mg/dl	<0.3 ml/kg/h >24 h, or anuria ×12 h

†Patients who receive renal replacement therapy are classified as stage 3.
sCr: Serum creatinine.

Table 2. Classification systems for acute kidney injury: Risk, Injury, Failure, Loss and End-stage Kidney classification.

Class	GFR criteria	Urine output criteria
Risk	Increased sCr ×1.5 or GFR decrease >25%	<0.5 ml/kg/h ×6 h
Injury	Increased sCr ×2 or GFR decrease >50%	<0.5 ml/kg/h ×12 h
Failure	Increased sCr ×3 or GFR decrease >75% or sCr ≥4 mg/dl with an acute rise >0.5 mg/dl	<0.3 ml/kg/h ×24 h, or anuria ×12 h
Loss	Persistent acute renal failure >4 weeks	–
End-stage kidney disease	End-stage kidney disease >3 months	–

GFR: Glomerular filtration rate; sCR: Serum creatinine.

Recent developments have proposed a number of novel biomarkers specific for early detection of kidney damage. These include neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, liver-type fatty acid binding protein (L-FABP) and kidney injury molecule-1 (KIM-1). NGAL protein is markedly induced during AKI. Schmidt-Ott *et al.* observed that NGAL levels rise within 3 h of kidney injury and often precedes by more than 24 h the rise in sCr [55]. A recent meta-analysis study by Haase *et al.* has confirmed its value as a diagnostic tool in cardiac surgical and critically ill patients [56]. L-FABP is a lipocalin, promoting oxidation of transported fatty acids in mitochondria and peroxisomes. Portilla *et al.* observed that urinary L-FABP levels increase within 4 h following cardiac surgery in AKI patients, but not in non-AKI patients [57]. In a recent prospective study of 374 patients undergoing CPB, Krawczeski *et al.* demonstrated that serum cystatin C levels were markedly increased at 12 h and remained elevated at 24 h following CPB in AKI patients, suggesting a correlation between cystatin C levels and renal dysfunction [58]. KIM-1 glycoprotein is another biomarker shown to improve early detection of postoperative AKI. Its sensitivity enhanced when measured in conjunction with other biomarkers [59].

Prevention

The mainstay of postoperative AKI prevention is optimal hydration, maintenance of adequate cardiac output and avoidance of nephrotoxins [60]. Many drugs have been trialled for renoprotection. N-acetylcysteine (NAC) is a free radical scavenger agent thought to inhibit inflammation and oxidative stress responses. NAC was demonstrated to reduce postoperative atrial fibrillation, however, it failed to protect against AKI following cardiac surgery [61]. Furosemide was shown to reduce tubular cell workload and decrease oxygen consumption, however, a meta-analysis conducted by Ho *et al.* failed to demonstrate improvements in mortality or reduced need for renal replacement therapy (RRT) [48,62]. Mannitol also failed to protect against renal injury in cardiac surgical patients [63,64]. To date, no single agent has been unequivocally proven to protect against renal failure following cardiac surgery.

Two novel agents that appear most promising and would benefit from further clinical trials are fenoldopam and natriuretic peptides. Fenoldopam, a selective DA-1 agonist, simultaneously decreases systemic vascular resistance and increases blood flow to the kidneys. A meta-analyses based on 16 RCTs reported that fenoldopam reduces the need for RRT and mortality in patients with AKI [65]. These findings are consistent with a systematic review by Patel *et al.* demonstrating the reduced need for RRT by 5% [66]. Atrial and brain natriuretic peptides induce natriuresis, which may prevent tubular obstruction, as well as improving glomerular perfusion, and they were found to reduce AKI [66,67].

Intraoperative strategies to avoid renal injury include maintaining adequate renal perfusion and oxygenation during CPB. Hematocrit level is a target parameter that can be optimized to improve renal function. Ranucci *et al.* observed that patients with a hematocrit level <26% and oxygen delivery <272 $ml.min^{-1}.m^{-2}$ during CPB are susceptible to developing postoperative AKI, which can be ameliorated by increasing pump flow to improve oxygen delivery [68]. Pulsatile flow was thought to improve end-organ perfusion by generating more hemodynamic energy, reducing vasoconstrictive reflexes, and increasing diffusion and oxygen consumption. Some authors found that pulsatile flow better preserved renal function when compared with standard linear flow, particularly in older patients [69,70], while others reported no difference in clinical outcomes between the two systems [71]. An evidence-based review by Alghamdi *et al.* concluded that there is currently insufficient evidence to support its routine use in clinical practice [72].

Trial of preoperative prophylactic dialysis in patients with known renal impairment has been attempted. Durmaz *et al.* randomized 44 patients with baseline sCr >2.5 mg/dl to prophylactic hemodialysis or hemodialysis when postoperative AKI was observed (control). The authors found that the operative mortality was significantly lower in the group receiving prophylactic dialysis, compared with the control group (4.8 vs 30.4%; p = 0.048). Additionally, postoperative AKI requiring dialysis dropped from 34.8% in the control group to 4.8% in the dialysis group [73]. A more recent prospective trial by Bingol *et al.* showed similar positive results in elderly patients undergoing cardiac surgery [74]. Sufficiently powered randomized trials will be necessary before this approach can be widely adopted.

Cerebral injury

Definitions & etiologies

Neurological morbidity represents the most disabling complication of cardiac surgery. Cerebral injuries following cardiac surgery are classified as type I (brain death, nonfatal stroke and new transient ischemic attack) and type II (neurocognitive dysfunction and encephalopathy) [75]. The more important subset of type I injuries is stroke, with an overall incidence of 1.6% after isolated CABG [76]. Less information is available on the incidence of type II injuries, but values as high as 50% have been quoted for patients with postoperative cognitive dysfunction (POCD) [75]. Risk factors for type I injuries include advanced age, previous neurologic event and proximal aortic atherosclerosis, whereas type II injuries are more likely in patients with hypertension, advanced age, pulmonary disease and excessive alcohol consumption [77].

Stroke patients commonly present with focal weakness and speech disturbance that lasts longer than 24 h [78]. Diagnostic imaging such as CT or magnetic resonance imaging (MRI) should be performed to detect possible mass lesion, acute intracerebral or subarachnoid hemorrhage. Patients with neurocognitive dysfunction often show impaired thought processes and behaviour with no focal neurological deficits. Various existing neuropsychological tests have been used to measure multiple cognitive domains, including memory, attention, language, executive functions and motor speed [76]. Finally, postoperative encephalopathy has been variably defined as confusion, combativeness, agitation, seizures, coma and prolonged alteration in mental status [79]. No definite cerebral lesions are found on CT scans in encephalopathic patients.

The main pathophysiological mechanisms underlying stroke include both macro- and micro-embolization and cerebral hypoperfusion [76]. Based on transcranial Doppler ultrasonography, Clark *et al.* demonstrated neurologic complications in 2.4% of patients with <30 microemboli and a staggering increase to 35% in those with >60 microemboli [80]. Similarly, Pugsley *et al.* demonstrated that the proportion of neuropsychological deficits rose from 8.6% of cases having <200 microemboli to 43% having >1000 microemboli [81]. Hemodynamically significant carotid stenosis has also been implicated. Naylor *et al.* reported that in predominantly asymptomatic patients, the stroke risk rose to 3% in patients with unilateral 50–99% stenosis, 5% with bilateral 50–99% and up to 11% with carotid occlusion [82].

Neurocognitive dysfunction and encephalopathy are not distinct entities but represent a spectrum of neurologic disorder with overlaps in the clinical features. Identified causal factors for type II injuries are somewhat overlapping with those for stroke. They include microembolization, intraoperative hypotension and prolonged oxygen desaturations. General anesthesia is another factor that is likely to contribute to cognitive decline. A randomized trial by Schoen *et al.* comparing sevoflurane-based with propofol-based anesthesia observed a greater incidence of cognitive dysfunction in patients assigned to propofol-based anesthesia [83].

Prevention

The main strategies applied to reduce neurologic injury following cardiac surgery involve thorough preoperative assessment of high-risk patients; careful intraoperative screening for aortic atherosclerosis; technical alteration; and, administration of pharmacological agents aimed at reducing cerebral embolic events.

Carotid artery duplex ultrasonography is now often included as part of routine preoperative cardiac work up. An extensive review by the American Academy of Neurology reported that in symptomatic patients, carotid endarterectomy (CEA) is highly beneficial for 70–99% stenosis, moderately beneficial for 50–69% stenosis and not beneficial for <50% stenosis. In the context of cardiac surgery, the optimum management of patients with concomitant carotid and coronary artery disease remains poorly defined [84]. To date, there are no randomized trials comparing outcomes of patients considered for simultaneous CEA and CABG versus staged CEA followed by CABG. The 2011 ACCF/AHA guidelines recommend the use of a multidisciplinary approach to therapy and assessment of patients with both symptomatic carotid and coronary artery disease [29].

Cross-clamping and cannulation of the ascending aorta may potentially dislodge unstable atheromatous plaques, causing a thromboembolic stroke. Identification of plaques before aortic manipulation is an important measure to assist surgical planning. Digital pal-

pation is the conventional screening technique, which could only detect 50% of aortic atheroma [85]. Transesophageal echocardiography (TOE) is useful, but provides limited visualization of the distal ascending aorta owing to the intervening main stem bronchus [86]. Epiaortic ultrasonography (EAS) has proved superior to both techniques in detecting potential atheromatous changes within the ascending aorta [85,86]. In a prospective review by Zingone *et al.* the use of EAS was associated with a reduced incidence of stroke from 3.3 to 1.9% in patients undergoing cardiac surgery [87].

Off-pump CABG has been proposed to reduce neurological risks by eliminating the adverse effects associated with CPB. However, this has not been borne out by randomized controlled trials [88,89]. One possible reason is that many so-called off-pump surgeries still involve manipulation of the aorta from partial aortic clamping for proximal graft anastomosis. In a study by Calafiore *et al.,* patients were divided into four groups, according to the degree of aortic manipulation: CPB with side-clamp; CPB with single-clamp technique; off-pump with side-clamp; and, off-pump with no aortic manipulation. The rate of postoperative stroke was 2.3, 1.2, 1.1 and 0.2%, respectively [90]. Similarly, Lev-Ran *et al.* observed a significant reduction in the incidence of stroke with the no-touch aortic technique in a study involving 700 off-pump CABG patients [91]. This demonstrates the importance of minimal aortic manipulation in reducing perioperative stroke risk.

Pulmonary injury

Definitions & etiologies

Pulmonary dysfunction remains a common and important complication after CABG. The manifestations of lung injury cover a wide spectrum, ranging from mild respiratory dysfunction to fulminant acute respiratory distress syndrome (ARDS). The incidence of ARDS is less than 2%, however, the mortality rate may be as high as 50% [92].

In recent years, the injurious effects of CPB on pulmonary function have been extensively investigated. CPB initiates a systemic inflammatory cascade, maintained by complement activation, neutrophil chemotaxis, cytokine production and arachidonic acid metabolites, which ultimately lead to pulmonary injury. In addition, concurrent absence of ventilation during lung deflation and diminished pulmonary perfusion during CPB lead to generation of free oxygen radicals with subsequent lung injury [93]. Despite the apparent pathological effects of CPB, the incidence of postoperative lung dysfunction following off-pump CABG was not significantly different from that of the conventional on-pump approach. Prospective randomized trials have shown a similar degree of change in perioperative alveolar–arterial oxygen gradients and arterial oxygen (paO_2) between on- and off-pump CABG [94,95]. Similarly, Cimen *et al.* showed no significant changes in the ventilatory function tests in both groups over six postoperative days [96].

Various other factors unique to cardiac surgery such as operative techniques, ITA dissection and myocardial hypothermia have also been implicated. Guizilini *et al.* compared lung function tests in 18 patients undergoing CABG by ministernotomy or conventional median sternotomy. The ministernotomy group showed better recovery of lung function than those subjected to median sternotomy [97]. Preservation of pleural integrity during retrieval of ITA was associated with lower incidence of postoperative atelectasis and pleural effusion [98].

Prevention

The contact between blood and synthetic surfaces of extracorporeal circuit is known to provoke a systemic inflammatory response. This has led to application of various biocompatible-coated circuits designed to mimic vascular endothelial surfaces, such as heparin, polymethoxyethyl acrylate, synthetic protein and phosphorylcholine, with heparin being the most extensively researched coating material. Compared with the standard uncoated circuit, de Vroege *et al.* demonstrated that heparin-coating significantly improves pulmonary indices as reflected by pulmonary shunt fraction, pulmonary vascular resistance index and PaO_2:FiO_2 ratio, as well as reduced inflammatory mediator release [99]. Recently, a large review by Mahmood *et al.* observed that a heparin-coated circuit improved biocompatibility, as reflected by platelet preservation, reduced leucocyte and complement activation, and proinflammatory cytokine production. Use of a heparin-coated circuit is also associated with reduced blood loss, reoperation rates, ventilation time, ICU and hospital stay [100]. However, the results should be interpreted cautiously given that the results were mostly derived from single-centered RCTs that are inadequately powered.

Ultrafiltration has been used in cardiac surgery as a means of removing excess fluid and limiting postoperative interstitial edema caused by hemodilution. In addition, it removes systemic inflammatory mediators that impair pulmonary function. Huang *et al.* found that the serum concentration of IL-6 and thromboxane B2 was effectively reduced by ultrafiltration with concomitant improvement in pulmonary compliance, gaseous exchange and airway resistance [101]. There are three existing ultrafiltration techniques that are applied, including conventional ultrafiltration (CUF), modi-

fied ultrafiltration (MUF) and zero-balance ultrafiltration. Perez-Vela *et al.* compared the benefits between CUF, MUF and combined strategy, and reported that the postoperative respiratory outcomes were similar in all three groups [102].

Hypoventilation during CPB is responsible for the development of microatelectasis and pulmonary edema, resulting in decreased pulmonary compliance [103]. To prevent this dysfunction, continuing mechanical ventilation during CPB has been proposed. After low-frequency ventilation during CPB, Imura *et al.* found that the pulmonary function expressed by oxygen tension, alveolar–arterial oxygen gradient and lactate dehydrogenase levels, improved with reduced tissue damage on lung biopsy [104]. A recent large analysis of studies, however, has shown that the clinical benefits of maintaining ventilation throughout CPB were short-lived with no improvement in patient outcome [105].

Due to the pivotal role that leukocytes play in systemic inflammatory response, leukocyte filtration during CPB was suggested as a way to limit pulmonary injury. A randomized study showed that the total leukocyte filtration resulted in a transient decrease in white cells following surgery. However, this effect did not correlate with improvements in respiratory index, intubation time or ICU stay [106]. An extensive review by Warren *et al.* evaluating the effectiveness of several leukocyte-depleting filters used in cardiac surgery observed small improvements in early postoperative pulmonary function, but did not result in clinical improvement (reduced hospital stay or mortality) [107].

There has been mounting interest in trialling pharmacological agents for the prevention and treatment of pulmonary lung injury. Corticosteroid is one of the earliest anti-inflammatory agents to be investigated in relation to pulmonary injury after CPB. The potential lung-protective effects of prophylactic corticosteroids remain controversial. Giomarell *et al.* reported improved pulmonary function in those receiving prophylactic corticosteroids. Furthermore, corticosteroid administration was shown to inhibit production of proinflammatory cytokines TNF-α, IL-6 and IL-8, while increasing serum levels of the anti-inflammatory cytokine IL-10 [108]. However, a large meta-analysis of 54 randomized studies by Dieleman *et al.* failed to demonstrate the beneficial effects of corticosteroids on pulmonary function in cardiac surgical patients. Thus, there is inadequate evidence to support its use within cardiac surgical practice [109]. Aprotinin, an antifibrinolytic agent, is also known to mitigate inflammatory response to CPB. Erdogan *et al.* reported significant improvement in forced expiratory volume and $paCO_2$ values in the aprotinin group compared with the control group, suggesting aprotinin had a pulmonary protective effect after cardiac surgery [110]. However, as mentioned above, a high incidence of morbidity (myocardial infarction, stroke, encephalopathy and renal dysfunction) and mortality were reported with aprotinin usage, resulting in its withdrawal from market in 2007 [11–13].

Intra-abdominal injury

The incidence of gastrointestinal (GI) complications has been reported in 0.12–12% of patients after cardiac surgery [111,112]. Mortality is highest for hepatic failure (74%), followed by bowel ischemia (71%), perforated ulcer (44%) and other intra-abdominal pathology such as pancreatitis, cholecystitis, GI bleeding, diverticulitis, paralytic ileus and bowel obstruction (11–27%) [113].

Postoperative GI complications are largely attributed to reduced splanchnic bed perfusion and oxygenation. Longer CPB times has been associated with inflammatory cascade activation, increased intestinal permeability, enhanced release of cytokines and microembolism, contributing to mucosal injury and subsequent GI organ damage [113,114]. Other factors such as perioperative hypotension, use of inotropes, postoperative arrhythmias, hemorrhage, nature of cardiac surgery and prolonged mechanical ventilation are also relevant [113,115].

Various potential strategies have been suggested to help improve splanchnic perfusion, including perioperative use of pharmacological agents (e.g., phosphodiesterase III inhibitors and dobumatine) and volume loading, modified conduct of extracorporeal circuit, and performing off-pump procedure [113]. However, due to the markedly low incidence of GI involvement, there is not enough evidence to support the proposed interventions. Therefore, early diagnosis and prompt treatment with close multidisciplinary collaboration are required when dealing with postoperative abdominal complications. It is beyond the scope of this article to cover all post-CPB GI complications, but the more common ones will be reviewed here.

GI bleeding constitutes nearly 31% of all intra-abdominal complications [113]. The majority of bleeding occurs in the upper GI tract. Those with previous history of peptic ulcer disease have an increased risk for developing GI hemorrhage after cardiac surgery. Interestingly, there is no significant causative link between conventional risk factors such as *Helicobacter pylori* infection and the development of stress ulcers in cardiac surgical patients [116]. A recent systematic review by Shin *et al.* suggests a trend toward reduced GI bleeding with routine use of acid suppression therapy. Additionally, proton-pump inhibitors were most effective in reducing the incidence of hemorrhagic gastritis and haematemesis [117].

Bowel ischemia constitutes nearly 18% of all intra-abdominal complications [113]. Majority of cases associated with cardiac surgery are caused by nonocclusive phenomena [118,119]. Preoperative patient characteristics, such as advanced age, end-stage renal disease and peripheral vascular disease, contribute to its development. Factors precipitating organ hypoperfusion after CPB include emergency operation, prolonged bypass, use of intra-aortic ballon pump and inotropic support [112,113]. The lack of characteristic clinical features in these very sick patients often make early diagnosis difficult. Abdominal distension, unexplained leukocytosis, persistent metabolic acidosis and hyperkalemia may be suggestive of bowel ischemia. Early utilization of arterial angiography and laparotomy should be considered in those with a high index of clinical suspicion [118,119].

Acute cholecystitis accounts for 11% of intra-abdominal complications [113]. Most cases are of acalculous variety. Multiple factors have been implicated in the development of acalculous cholecystitis, including increased bile viscosity, visceral hypoperfusion and the release of cytokines (factor XII and platelet-activating factor) [120]. Early diagnosis is similarly challenging, as the clinical presentation may be variable. Ultrasonography remains the gold standard in the evaluation of acalculous cholecystitis. Both conservative management and surgery have been advocated for the treatment of this condition following cardiac surgery.

Conclusion

Over recent decades, CABG has evolved to become the most successful and widely performed cardiac operation. Significant technological advances have made this possible. Both mortality and morbidities have steadily declined over the years. The noncardiac complications discussed in this paper are fairly uncommon, occurring in only a few percent of patients undergoing CABG, but with potentially devastating consequences. Most of these complications are multifactorial in etiology and, therefore, a multifaceted approach is required for their prevention and treatment.

Future perspective

CABG remains the treatment of choice for complex multivessel coronary artery disease. Continuing improvements in technology are likely to see more CABGs being performed through minimally invasive approaches with or without the utilization of the heart–lung machine. Techniques such as anaortic off-pump CABG will have the potential of reducing perioperative stroke risk. Total arterial revascularization, particularly with the use of bilateral *in situ* internal thoracic arteries, is likely to be increasingly utilized. This coupled with improved secondary prevention will undoubtedly continue to improve the outcomes of CABG patients in the coming decade.

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