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Effects of inflammation and oxidative stress on postoperative delirium in cardiac surgery

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The past decade has witnessed unprecedented medical progress, which has translated into cardiac surgery being increasingly common and safe. However, complications such as postoperative delirium remain a major concern. Although the pathophysiological changes of delirium after cardiac surgery remain poorly understood, it is widely thought that inflammation and oxidative stress may be potential triggers of delirium. The development of delirium following cardiac surgery is associated with perioperative risk factors. Multiple interventions are being explored to prevent and treat delirium. Therefore, research on the potential role of biomarkers in delirium as well as identification of perioperative risk factors and pharmacological interventions are necessary to mitigate the development of delirium.

Introduction

Postoperative delirium (POD) is a common acute neurocognitive disorder after cardiac surgery characterized by cognitive decline, fluctuating mental status, impaired consciousness, inattention, or confusion, resulting in severe consequences for patients (1). Although delirium occurs in patients of all ages, current evidence suggests it is most likely to occur in elderly patients with preoperative chronic central nervous system disease. It has been reported to affect 20–30% of elderly patients admitted to the hospital on an emergency basis and can result in varying degrees of adverse outcomes, including functional decline, permanent cognitive decline and mortality (2). During clinical practice, the incidence of POD in patients undergoing general surgery is 10-46%, while it can reach 50–67%

in patients after cardiac surgery (3–5). In addition, the incidence of POD can reach up to 72%, depending on the type of heart surgery (6) (**Table 1**). POD is detrimental to neuronal activity metabolism and leads to long-term cognitive decline, functional degeneration, and poor prognosis (7, 8). An increasing body of evidence suggests that older age, preoperative cognitive impairment, type of perioperative medication administered, and preoperative conditions, including anemia, electrolyte abnormalities, dehydration and malnutrition, are risk factors for POD (9–13). Although the risk factors associated with delirium are well established, the pathogenesis of its occurrence is not well understood, thus hindering the development of effective prevention and treatment of delirium. Interestingly, it is widely thought that cardiopulmonary bypass (CPB) in cardiac surgery is a primary activator of the inflammatory response (14, 15). Previous studies reported that the potential pathogenesis of delirium might include acute central cholinergic deficiency, oxidative stress, decreased GABA-ergic activity, abnormal melatonin and serotonin pathways, noradrenergic hyperactivity, neuroinflammation leading to neuronal damage, and cerebral hypoperfusion (16–18). The purpose of this review is to discuss the pathophysiology of delirium after cardiac surgery, risk factors, and the potential role of pharmacological interventions that may reduce postoperative delirium.

Pathophysiology

The underlying mechanisms behind delirium are unclear. Many hypotheses exist for the pathophysiology of delirium, such as neuroinflammation and oxidative stress. There is growing evidence that different factors, such as underlying preoperative diseases associated with inflammation, such as cardiovascular disease and diabetes, surgical trauma, extracorporeal circulation, and organ reperfusion injury during cardiac surgery, can lead to a complex inflammatory response. Therefore, we will describe the various sources of perioperative inflammation from cardiac surgery (**Figure 1**).

Sources of inflammatory response in cardiac surgery

Inflammatory state

As a result of population aging, the incidence of cardiovascular disease in the elderly has significantly increased. Nowadays, many elderly patients undergo cardiac surgery of varying complexities (34). However, cardiac surgery patients are often associated with various underlying preoperative comorbidities, such as localized regional or systemic atherosclerosis, diabetes, and pulmonary and kidney diseases, which are related to abnormal redox status and oxidative

stress (35, 36). Current evidence indicates that atherosclerosis is a chronic inflammatory disease with an autoimmune component (37). In addition, it has been established that risk factors contributing to atherosclerosis, such as diabetes and dyslipidemia, promote the inflammatory response in blood vessels and indirectly increase atherosclerotic (38, 39). Although it has been shown that atherosclerotic coronary artery disease requiring intervention is related to pre-procedural oxidative stress and inflammation and is significantly exacerbated during CPB (40), this chronic disease associated with the inflammatory response has not attracted significant interest from the scientific community, probably because many of these inflammatory markers are not suitable for routine risk assessment (41).

Systemic inflammation associated with cardiopulmonary bypass

During cardiac surgery, various factors can lead to the development of both systemic and non-systemic inflammatory responses. At the same time, injurious processes may also trigger the onset of the systemic inflammatory response during surgical trauma. Furthermore, this inflammatory response leads to synaptic damage, neuronal dysfunction and death, and neurogenesis disorders (42). The most crucial factor leading to systemic inflammatory response is CPB. It has been shown that CPB in cardiac surgery causes an intense inflammatory response through various mechanisms (14, 43), including primarily blood contact with foreign surfaces of the CPB circuit, surgical trauma and endotoxemia (44). Inflammatory responses associated with CPB include activation of coagulation factors, platelets and fibrinolysis, elevation of inflammatory cytokines including interleukin (IL)-1, IL-6, and tumor necrosis factor-α, and activation of endothelial cells and leukocyte responses (45). In addition, a previous study found that patients experiencing CPB demonstrated augmented expression of leukocyte-mRNA not only for pro-inflammatory cytokines, CAMs (i.e., platelet endothelial cell adhesion molecule-PECAM) but also for IL-10 and heme oxygenase-1 (46). In addition to CPB, several factors can cause an inflammatory response, including reperfusion of significant organs after ischemia, endotoxin released from the inflamed gut, and mechanical surgical trauma (47). Furthermore, some studies found that global injury from CPB and cardiac arrest and localized injury from non-CPB can cause cardiac ischemia-reperfusion injury, while myocardial reperfusion injury activates neutrophils, triggering an inflammatory response (48).

Inflammatory response during myocardial ischemia and reperfusion

Ischemia and reperfusion are pathological conditions whereby the recanalization and reoxygenation of blood flow

TABLE 1 A comparison of the incidence of delirium after different cardiac procedures.

Study	Study design	Surgery type	Sample size	Age, year	Outcome measurement	Delirium assessment tool	No. of patients with POD
Li et al. [19]	Retrospective	CABG	1426	71.28 ± 4.768	ICU stay time	CAM-ICU	560 (39.3%)
Lecho wicz et al. [20]	Retrospective	CABG	1098	65.5 ± 9.8	1-year and 1month mortality; ICU stay time and hospitalization time	CAM-ICU	164 (14.9%)
Brown et al. [21]	Prospective	CABG	66	69.6 ± 7.4	Hospital mortality; Hospital days; ICU time	CAM/CAM-ICU	37 (56.1%)
Norkie ne et al. [22]	Prospective	CABG	1367	65.0 ± 9.2	Hospital mortality; ICU stay time; Mechanical ventilation time	DSM	42 (3.1%)
Liu et al. [23]	Retrospective	AD (Type- A)	100	51.90 ± 9.65	ICU stay time	CAM-ICU	34 (34%)
Cai et al. [24]	Retrospective	AD (Type- A)	301	50.66 ± 12.24	Hospital mortality; Hospital days; ICU time	CAM-ICU	73 (24.25%)
Liu et al. [25]	Retrospective	AD (Type- B)	517	53.2 ± 10.9	Hospital days; ICU stay time	CAM-ICU	69 (13.3%)
He et al. [26]	Retrospective	AD (Type- A)	438	57.89 ± 12.41	ICU stay time	CAM/CAM-ICU/RASS	78 (17.8%)
Humbe Rt et al. [27]	Prospective	SAVR	27	82.1	Hospital days	CAM	8 (30%)
Rao et al. [28]	Prospective	SAVR	77	81.3 ± 6.4	Hospital days	MMSE/CAM	39 (50.7%)
Shi et al. [29]	Prospective	SAVR	77	77.9 ± 5.3	Hospital days	CAM/CAM-S	39 (60.7%)
Wesselink et al. [30]	Retrospective	TAVR	675	77-85	Hospital days	DOS	93 (14%)
Van der Wul et al. [31]	Prospective	TAVR	703	75-84	30-days to 5years mortality	DSM	116 (16.5%)
Goudz waard et al. [32]	Prospective	TAVR	543	79.1 ± 8.0	1years mortality	DSM	75 (14%)
Körber et al. [33]	Prospective	MVR	177	72-82	ICU stay time	CAM-ICU	16 (9%)

CABG, coronary artery bypass graft; AD, aortic dissection; SAVR, surgical aortic valve replacement; TAVR, transcatheter aortic valve replacement; MVR, mitral valve repairment; ICU, intensive care unit; POD, postoperative delirium; CAM, Confusion Assessment Method; CAM-ICU, Confusion Assessment Method for ICU; MMSE, Mini-mental State Examination; DOS, Delirium Observation Scale; RASS, Rating Sedation Scale.

are usually associated with increased tissue damage and inflammatory response, called reperfusion injury [49]. The earliest feature of cardiomyocyte ischemia is the depletion of intracellular ATP. The reduction of molecular oxygen inhibits the coupling between the respiratory chain and oxidative phosphorylation and inhibits ATP synthesis. Therefore, cellular ischemia and hypoxia disrupt the balance between energy production and utilization, and roughly 95% of the energy produced by mitochondrial oxidative metabolism is stored in the ATP molecule, which is essential for the heart's metabolic activities and mechanical functions. During cellular ischemia, mitochondrial energy decreases production and is accompanied by abnormal accumulation and depletion of several intracellular metabolites, including a rise in intracellular calcium ions and lactate and a decline in ATP levels. Ample evidence substantiates

that ATP depletion increases cardiomyocyte membrane permeability and intracellular calcium ion concentration and drives the activation of calcium-dependent phospholipase and proteolytic enzymes, which may affect endothelial production, cell oxygen radical production and leukocyte-endothelial interactions [50–52]. Myocardial reperfusion injury leads to inflammation and oxidative stress and produces various inflammatory cytokines and reactive oxygen species (ROS), inhibiting cardiac function and apoptosis [53]. Many experimental models found that the myocardium produces IL-6 during ischemia-reperfusion injury [54, 55]. Besides IL-6, some inflammatory factors can be generated to a certain extent in the heart. For instance, IL-8 release during myocardial ischemia can stimulate the upregulation of adhesion molecules on different cell types [56]. Besides the above pro-inflammatory factors,

FIGURE 1
The source of inflammatory response in cardiac surgery and its effect on POD.
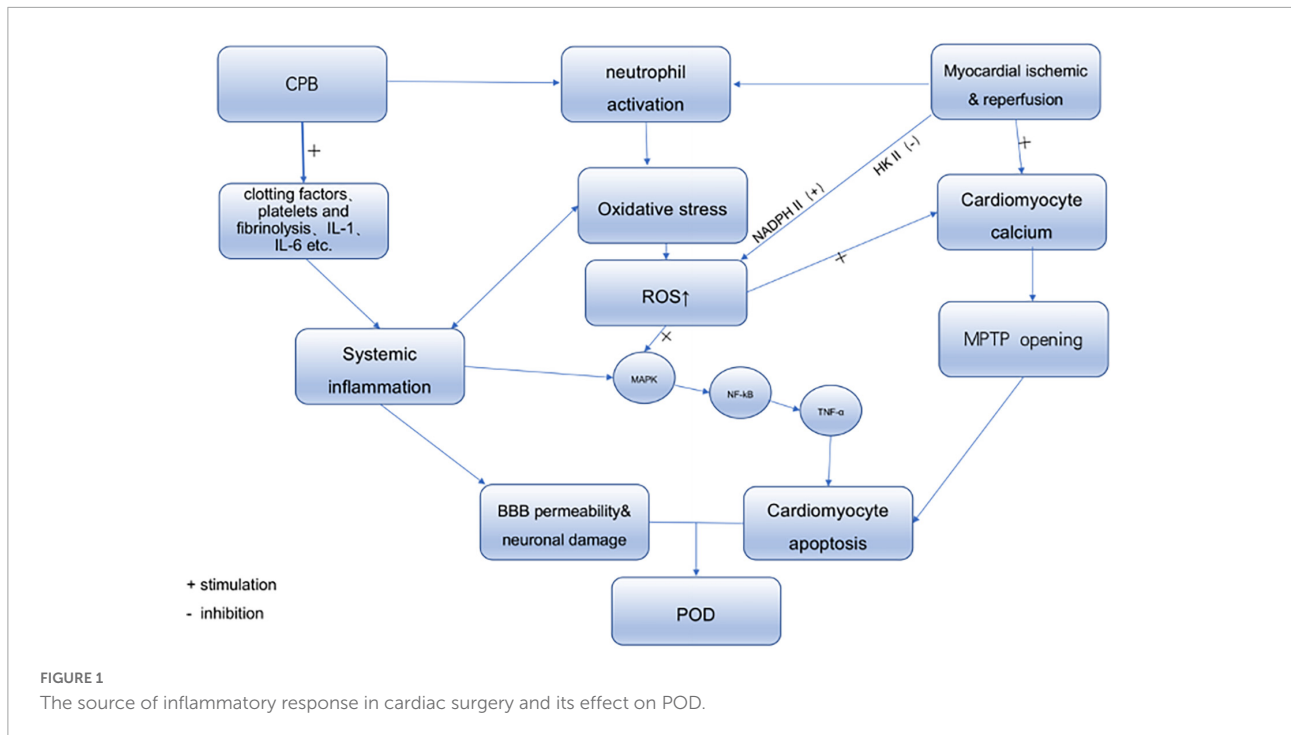
cardiomyocytes produce IL-18 and IL-1 pro-inflammatory cytokines (57–59). In addition, heart cells produce anti-inflammatory factors like IL-10 (60). Hence, cardiomyocytes are a source of inflammatory factors and markers, especially during ischemia-reperfusion injury.

Inflammation and the pathogenesis of postoperative delirium

Effects of different inflammatory factors on cardiac performance

It has been established that cytokines, including pro- and anti-inflammatory factors, can either damage or protect the myocardium during inflammation. Moreover, these effects can be achieved by acting directly on cardiomyocytes or altering the levels of cardiac injury markers. IL-6 production has been associated with adverse inotropic effects, myocardial stunning, and reduced neutrophil infiltration (61–63). It has been suggested that myocardial depression is associated with increased nitric oxide (NO) production, increasing intracellular cyclic guanosine monophosphate and activating cyclic guanosine monophosphate-dependent protein kinase to inhibit L-type Ca^{2+} channels inducing adverse inotropic effects (64, 65). In addition to IL-6, IL-8 locally generated in the heart exacerbates cardiac injury by enhancing leukocyte activation and aggregation. Another cytokine, IL-18, can

reportedly promote the activation of pro-apoptotic signaling pathways and induce endothelial cell death (66). Besides the pro-inflammatory markers described above, anti-inflammatory markers also influence cardiac function. For instance, IL-10 may attenuate reperfusion injury via inhibiting neutrophil infiltration into the myocardium (60). Furthermore, increased inflammatory markers, chemokines, and some inflammatory markers are often accompanied by endothelial dysfunction and blood-brain barrier (BBB) disruption (67). Neuroinflammation can cause neuron damage in the brain and concomitant microglial activation leading to delirium (68).

Inflammatory response and factors that affect the occurrence of postoperative delirium

Although the exact mechanisms of delirium onset remain unclear, there are multiple hypotheses regarding its pathophysiological mechanisms, of which neuroinflammation has attracted the most attention. During cardiac surgery, stress factors such as CPB, surgical trauma and ischemia-reperfusion injury lead to significant inflammation, which also provides a pathway for neuroinflammation processes. POD has long been thought to respond to physiological disorders caused by CPB management, explaining the term "pump-head" (69–71). However, recent studies revealed similar POD incidence and inflammatory marker levels, irrespective of CPB use during the surgical procedure (71–75). Hence, it has been demonstrated

that avoiding CPB does not improve cognitive functions. CPB itself can trigger SIRS, which contributes to BBB leakage and the development of neuroinflammation (73, 76, 77), as well as also can activate pro-inflammatory factors produced by macrophages and monocytes to increase BBB permeability and change neurotransmission, which may play a key role in causing POD (78). To verify whether SIRS is involved in POD, the optimal steroid type dose and administration time, i.e., dexamethasone, 0.1 mg/kg, 10 h before surgery, have been determined (79). Indeed, inflammation may play a crucial role in long-term cognitive function. However, there is still an urgent need for more research in this area to determine its exact role.

Oxidative stress during cardiac surgery

Redox signaling is involved in changes in ROS levels and various processes, such as stress response pathways, homeostasis and cardiac remodeling and fibrosis (80–83). ROS are a natural by-product of the normal oxygen metabolism process produced in mitochondria where aerobic metabolism occurs. It is well-recognized that cells use various defense mechanisms to protect themselves from ROS. However, ROS levels increase more dramatically during stress or inflammation than endogenous antioxidant capacity, leading to oxidative stress, thereby causing substantial damage to many cellular molecules (80, 81, 84). Preoperative coronary atherosclerosis, diabetes mellitus, and related kidney and lung diseases have been associated with oxidative stress, which can be severe during CPB (40).

Of reactive oxygen species during surgery

Mounting evidence substantiates that during cardiac surgery, the body produces large amounts of unstable free radicals (85). Under physiological conditions, ROS and nitrogen can act as messengers for normal cellular functions. However, under oxidative stress conditions, they can disrupt intracellular Ca^{2+} homeostasis and lead to cell death (86). Different coagulation and pro-inflammation pathways, activation of the survival cascade and altered redox status are related to CPB (87–89). Although significant improvements have been made over the years in cardiac surgery, oxidative stress and inflammation remain significant issues to be addressed in the CPB period (90, 91). As described above, during CPB, hemolysis, ischemia-reperfusion injury, and neutrophil activation exert a crucial effect on the activation of oxidative stress and associated pro-inflammatory and pro-apoptotic signaling pathways, affecting multiple organs, including the cardiac myocardium, lung, and kidney, as well as influencing clinical outcomes. Importantly, the primary source of ROS in cardiac surgery under CPB is

neutrophils (92), which are activated by cytokines from the systemic circulation, coronary vessels, and cardiomyocytes. For example, cytokines can stimulate the upregulation of adhesion molecules on cardiomyocytes, causing neutrophils to adhere and release ROS and proteolytic enzymes (56).

In contrast, the myocardium produces ROS during ischemia-reperfusion injury (53), mainly through activation of NADPH oxidase 2, and increases mitochondrial ROS through metabolic overload and reduced hexokinase II binding on mitochondria (93). In addition, ROS can promote nitrosylation, carbonylation, disulfide bond formation and glutathionylation to regulate the activity of signaling proteins, thereby inducing the activation of pro-inflammatory and pro-apoptotic signaling pathways, such as MAPK and NF-κB signaling pathways, and leading to cytoskeleton disruption and cell tube damage (94–97) (Figure 2).

Reactive oxygen species mediate the pathogenesis of postoperative delirium
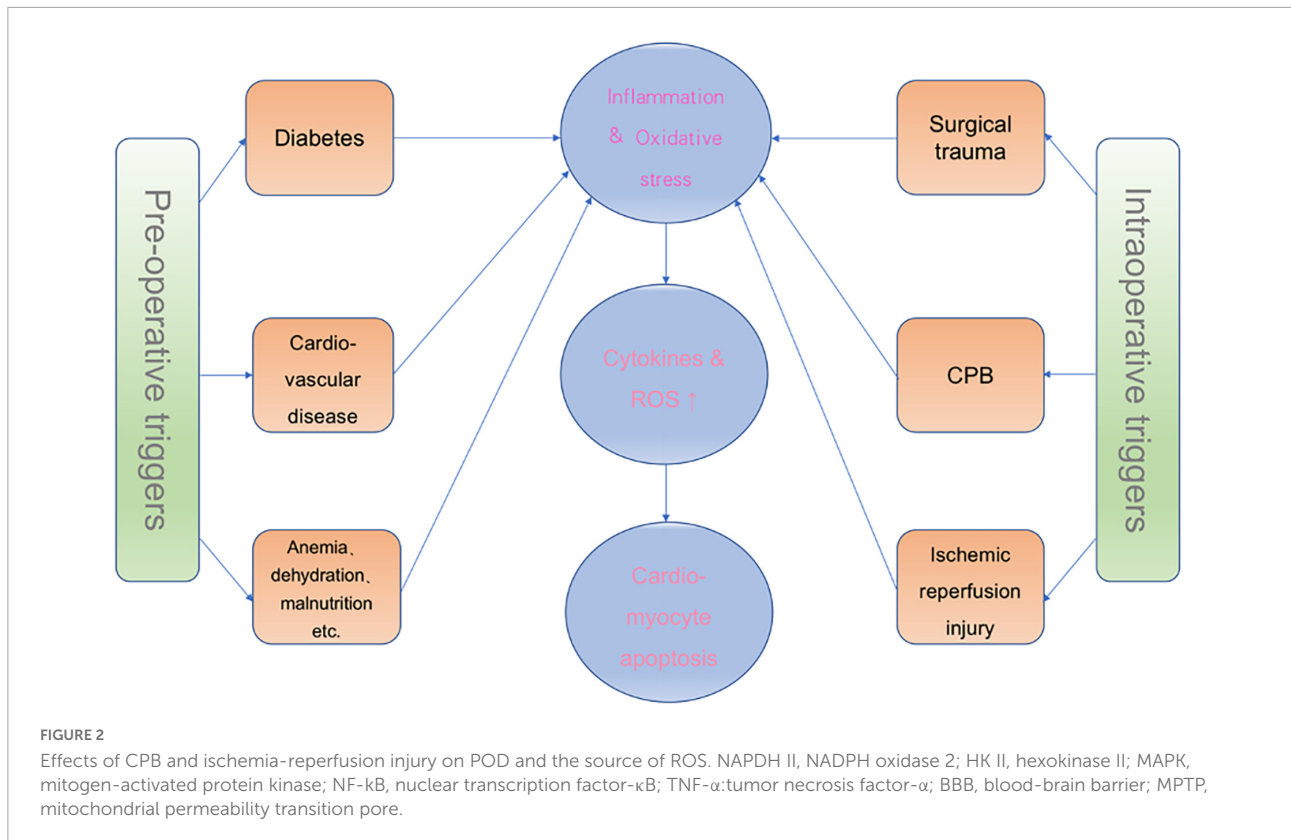
During surgery, especially during CPB and ischemia-reperfusion injury, the levels of ROS are markedly increased while the antioxidant capacity is decreased (98). Recent studies have shown that decreased antioxidant capacity is an essential feature of conditions such as major depression and cognitive impairment. Besides, it has been documented that patients with cerebrovascular or psychiatric diseases have low plasma antioxidant capacity (99, 100), and oxidative stress mediates neuronal damage (101, 102).

Perioperative risk factors

Many risk factors are associated with postoperative delirium. While some may predispose patients to delirium, other risk factors precipitate delirium such as medications given during the perioperative period. Predisposing factors must be considered when performing treatment in the clinical setting, especially in patients already at high risk for postoperative delirium. For controllable risk factors, optimization should be performed in the perioperative period. Based on evidence and consensus statements of the European Society of Anesthesiology guidelines (103) and other studies, we propose some perioperative risk factors that may contribute to postoperative delirium and are listed in Table 2.

Preoperative risk factors

A great number of current studies have shown that advanced age is a recognized independent risk factor for postoperative delirium and that the risk of POD increases progressively

FIGURE 2
Effects of CPB and ischemia-reperfusion injury on POD and the source of ROS. NAPDH II, NADPH oxidase 2; HK II, hexokinase II; MAPK, mitogen-activated protein kinase; NF-κB, nuclear transcription factor-κB; TNF-α:tumor necrosis factor-α; BBB, blood-brain barrier; MPTP, mitochondrial permeability transition pore.

with age (13, 104). In a meta-analysis by Chen et al. (105), preoperative carotid stenosis, diabetes mellitus, hypertension, left ventricular ejection fraction percentage, preoperative cognitive impairment, and NYHA class III or IV were found to be risk factors for postoperative cardiac delirium. Among them, a study by Junichiro Miyazaki et al. found that carotid plaque > 50% was a significant predictor of postoperative stroke or transient cerebral ischemia (TIA) or delirium in cardiac surgery (non-extracorporeal CABG). In addition to this, a study by Trabold et al. (13) found that preoperative anemia, dehydration, electrolyte abnormalities and signs of malnutrition were also risk factors for postoperative delirium. However, it remains to be elucidated whether intervention of these risk factors before surgery affects the outcome of delirium, and therefore, a large number of studies should be needed to investigate whether preoperative prevention and optimization of these risk factors has an impact on the incidence of delirium after cardiac surgery.

Intra- and postoperative risk factors

Whether the duration of CPB contributes to delirium after cardiac surgery and yielded conflicting results. Several studies have found an independent association between CPB duration and POD (106, 107), such as in a study by O'neal

et al. (107), which found that CPB duration was associated with a significantly increased risk of delirium in patients who underwent CABG. Whereas in Smith et al. (108) retrospectively examined 12 studies related to this issue and found that six studies resulted in postoperative delirium; five found no effect and one study found a negative association. The duration of CPB depends on the complexity of the procedure, procedures with higher complexity have an increased incidence of postoperative delirium. The incidence of delirium is higher in valve surgery and CABG compared to valve replacement or repair, and higher in more complex procedures such as replacement of multiple valves, aortic reconstruction, and deep hypothermic extracorporeal circulation. Whether valve surgery itself causes an increased rate of cerebral embolism leading to a higher incidence of POD or whether the length of surgery or CPB causes POD is unknown and therefore requires more research to explore and confirm. In addition, Whether the presence or absence of extracorporeal circulation in coronary artery grafting affects the incidence of postoperative delirium has been a question that many scholars have tried to investigate and explain. It is well known that during the period of CPB, the direct exposure of blood to the foreign body surface activates immune mediators, as well as CPB-induced leukocyte/platelet activation, procoagulation and fibrinolysis mediated by thrombin/fibrin, leading to elevated proinflammatory mediators and activation of

TABLE 2 Perioperative risk factors for delirium after cardiac surgery.

Preoperative risk factors	Intra-postoperative risk factors
Age ≥ 60 years	CPB time
Preoperative co-morbidities (cerebrovascular diseases such as stroke, carotid stenosis, TIA; atrial fibrillation, diabetes, anemia, depression, Parkinson's, dementia)	Type of surgery Intraoperative bleeding (transfusion of red blood cells and platelets)
Frailty (malnutrition, hypoalbuminemia, hypercholesterolemia, high levels of inflammation, muscular atrophy, etc.)	Hypothermia
Prolonged preoperative fasting and dehydration	Emergency surgery
Hearing impairment and visual impairment	Depth of anesthesia and medications
Chronic alcohol/substance abuse	Pain

TIA, Transient ischemic attack, CPB, Cardiopulmonary bypass.

systemic inflammatory response, thus CABG surgery triggers a complex pro-thrombotic and pro-inflammatory response which is thought to damage the BB, leading to neuroinflammation and consequent neurological dysfunction. The off-pump CABG procedure, on the other hand, is thought to trigger a lesser inflammatory response than CABG due to the absence of CPB. The current study reports conflicting results for the two surgical modalities on POD, with Gaudino's (109) study finding no significant difference in the incidence of postoperative delirium between CABG under non-extracorporeal and extracorporeal circulation. In contrast, in a study by O'neal et al. (107), the duration of CPB was found to be associated with a significantly increased risk of delirium in patients receiving CABG. Therefore, more clinical experimental studies are needed to explore and confirm this. Intraoperative transfusion of hemoglobin and platelets can also affect the postoperative morbidity. It is well known that the input of processed and stored blood products can cause severe systemic inflammation. Studies have found (110), that perioperative blood transfusion is an independent risk factor for postoperative delirium. In addition to this, several studies (111, 112), have shown that there is an independent risk factor for POD during perioperative allogeneic transfusion and that there is a dose-dependent relationship between the amount of blood transfused and the risk of POD.

Due to the specificity of cardiac surgery, the requirements of hypothermia need to be met during the procedure, and prolonged and sustained hypothermia can induce burst suppression of the EEG. In addition, the depth of anesthesia gradually increases as the temperature decreases, and perioperative neurodetectors commonly used in cardiac surgery, such as cerebral oxygen saturation or EEG detectors (i.e., dual-frequency index BIS), have been shown to help predict postoperative delirium. In recent years, many studies (113–115) have demonstrated the effect of anesthetic depth monitoring on neurological complications such as POD, POCD, and cerebrovascular accidents. A study by Perez-Otal (116) found that obtaining adequate anesthetic depth through intraoperative neuromonitoring and adjusting the anesthetic dose to avoid overuse of anesthetic drugs helped improve postoperative cognition in the elderly. Cardiac surgery is commonly associated with postoperative pain due to large surgical invasions and surgical indwelling tubes. Pain causes an acute stress response and an immediate cognitive burden (117) and increases the risk of other postoperative complications, such as pulmonary atelectasis, which may also contribute to POD. A study by Subramaniam (118) found that postoperative administration of analgesic drugs combined with sedative drugs significantly reduced the incidence of in-hospital delirium in elderly patients undergoing cardiac surgery.

For cardiac surgery, perioperative neurological dysfunction caused by brain injury, in addition to delirium, stroke is a topic that has generated much debate among scholars. The three major causes of neurologic dysfunction and injury during cardiac surgery are microemboli, hypoperfusion, and a generalized inflammatory reaction. Many intraoperative strokes are the result of the embolization of atherosclerotic material from the aorta and brachiocephalic vessels. In addition to this, air and fat emboli blocking blood vessels can also cause neuronal damage. The important principles to reduce emboli are anticoagulation, filtration of blood, removal of air and avoidance of atherosclerotic emboli. Many intraoperative monitoring modalities are available to reduce the occurrence of such risks, such as TEE to help surgeons determine the optimal aortic cross-clamping and cannulation position, which can be effective in avoiding potential embolization of atherosclerotic plaques, and intravenous reservoirs and arterial line filters in CPB circuits to effectively eliminate air and fat emboli. Various brain protection techniques are also used during cardiac surgery, including hypothermia, cerebral perfusion modalities, and pharmacological protection. Maintaining optimal cerebral perfusion by maintaining MAP at a perfusion pressure within the autonomic range of the brain during surgery may also be an important component in reducing brain injury. In addition to this, lowering brain temperature may reduce cerebral blood flow and excitotoxicity to protect against ischemic neuronal injury. There are no clear guidelines for the prevention of intraoperative stroke, but some intraoperative monitoring strategies may help to avoid stroke. In general, non-pharmacological strategies include monitoring of brain oxygenation and perfusion with devices such as near infrared spectroscopy and Transcranial Doppler help. Epiaortic and transesophageal echocardiography visualize aorta pathology, enabling the surgeon to sidestep atheromatous segments. Additionally can the use of specially designed aortic cannulae and filters help to reduce embolization. Brain perfusion can be improved by using antero- or retrograde

cerebral perfusion during deep hypothermic circulatory arrest, by tightly monitoring mean arterial blood pressure and hemodilution. Controlling perioperative temperature and glucose levels may additionally help to ameliorate secondary damage. For perioperative neurological dysfunction caused by brain injury after cardiac surgery, current studies suggest that microemboli, hypoperfusion and systemic inflammatory response are the results. Among them, embolic occlusion and cerebral hypoperfusion are considered to be important causes of intraoperative stroke. Although the risk factors for causing POD are currently identified as being very similar to those for stroke, efforts to link the extent of for emboli and POD have been inconsistent.

Preoperative interventions and management

The function of related anti-inflammatory agents and antioxidants in reducing postoperative delirium

Parecoxib

Parecoxib is a non-steroidal anti-inflammation drug that can selectively block the effect of cyclooxygenase-2 (COX-2) and can be rapidly converted to the active metabolite valdecoxib in the body. It is widely used clinically in treating osteoarthritis, rheumatoid arthritis, and postoperative pain relief (119, 120). A recent study (121) showed that parecoxib has neuroprotective effects. Some studies have found that treatment of primary cultured rat astrocytes with H_2O_2, a strong oxidizing agent, led to oxidative damage and was used to establish an oxidative stress model. These results substantiated that parecoxib exerts a protective effect against H_2O_2-induced oxidative damage in rat astrocytes, and its mechanism of action may be related to a reduction in cellular ROS levels, a decrease of apoptosis rate, inhibition of aquaporin-4 (AQP4) expression, a decrease of b-cell lymphoma-2 (Bcl-2) associated X protein (Bax) expression, and increase of BCL-2 and brain-derived neurotrophic factor (BDNF) expression.

Statins

Statins are HMG-CoA reductase inhibitors with pleiotropic effects, including anti-inflammatory, antioxidant, immunomodulatory, and antithrombotic properties (122–124). It is well-established that statins modulate the expression of pro-inflammatory factors such as IL-8, IL-6 and monocyte chemoattractant protein-1 (MCP-1) levels, thereby exerting anti-inflammatory and cardioprotective effects during cardiac surgery (125). Intriguingly, statins can modulate NAPDH oxidase enzyme activity, thus attenuating ROS production and exerting an antioxidant effect (126). An observational study by Katznelson et al. (127) found that preoperative administration of statins was associated with a reduced risk of POD by analyzing 1059 patients undergoing cardiac surgery with CPB, and the protective effect on POD was more pronounced in patients ≥60 years of age. However, some studies (128, 129) found no association between preoperative statin administration and POD after CPB by analyzing IL-1, T-α and C-reactive protein levels in patients undergoing coronary artery bypass grafting (CABG) surgery. To account for this controversial effect of statins on POD, some researchers proposed multifactorial and complex pathogenic mechanisms that cause POD (e.g., embolic events occurring in CPB, cardiac output and hypoperfusion and hypoxic events, and prolonged postoperative ICU stay can inhibit the anti-inflammatory effects of statins) (8, 129–132). Therefore, the protective effect of statins on POD in cardiac surgery has not been clearly defined, emphasizing the need for more studies.

Melatonin

Melatonin is a natural hormone produced by the pineal gland in the brain, synthesized from tryptophan and has been established to participate in sleep-wake cycle regulation (133). Melatonin production reportedly quickly declines with age and can exert antioxidant effects by scavenging free radicals, stimulating endogenous antioxidant enzymes, improving the efficiency of other antioxidants, and protecting mitochondria from oxidative stress by affecting mitochondrial membrane potential (134, 135). In addition, a growing body of literature suggests that melatonin exerts anti-inflammatory effects in acute or chronic inflammatory processes (136). In the study by El-Shenawy and Carrasco (137, 138), it was found that in rats pretreated with melatonin, the inflammatory response and the levels of pro-inflammatory factors, such as IL-1β and TNF-α, were decreased, while the levels of anti-inflammatory factor IL-4 were increased. The above factors suggest a potential role of melatonin in POD (139). A meta-analysis by Asleson et al. (140) suggested an association between melatonin and POD prevention. Although contradictory findings have been reported in the literature, the lack of validity may be due to sampling size effects. Therefore, larger sample sizes and more complex randomized controlled trials are needed to determine the efficacy of melatonin on POD.

Dexmedetomidine

Dexmedetomidine (DEX) is a potent α2-adrenoceptor agonist and a common and vital adjunct during general anesthesia. In addition to a low hemodynamic impact, it can reduce the dose of intraoperative anesthetic and analgesic drugs and improve patient comfort postoperatively (141). Recent studies have demonstrated that DEX can exert anti-inflammatory effects by reducing the expression of various

pro-inflammatory factors while protecting organ tissues from injury (142, 143). In addition, DEX may alleviate central nervous system (CNS) damage through antioxidant effects (144). Animal experiments by Wu and Hu et al. (145, 146) have reported that DEX provides neuroprotective effects and improves cognitive function after cardiac surgery. Besides, a meta-analysis of 26 randomized controlled trials by Wan et al. found that peri-operative DEX treatment in patients undergoing general anesthesia could significantly reduce the incidence of POD and inflammation compared with controls (147). Overall, DEX exhibits therapeutic effects against POD and inflammation.

Conclusion

Postoperative delirium (POD) is a common complication after cardiac surgery and can affect patient survival and mortality. Although many risk factors have been established regarding POD, the molecular mechanisms of the development of delirium are not fully understood. Current evidence suggests that inflammation caused by preoperative disease status, CPB, and ischemia-reperfusion injury may lead to delirium. Indeed, more research and randomized experiments in this field are warranted to confirm and provide new ideas for the clinical treatment of POD. Although the precise cellular mechanisms and pathways for POD occurrence are still difficult to resolve. Some perioperative interventions and pharmacological prophylaxis have shown promising results for the improvement of delirium. However, more work needs to be done before they can be routinely incorporated into clinical practice. In particular, a better understanding of the role in the development of POD is an important step toward developing more effective treatments and optimizing the conditions for anti-inflammatory and antioxidant-based therapeutic interventions. Eventually, this review also has some limitations. There is a large body of literature describing the possible relevance of inflammation and oxidative stress to POD, but in some studies the relationship between these factors was found to be inconsistent. However, some perioperative interventions and pharmacological prophylaxis have shown good results

in improving delirium, and it is certain that POD has a complex association with inflammation and oxidative stress. Therefore, more work is needed before they can be routinely incorporated into clinical practice, especially in the development of more effective therapeutic approaches and in the optimization of conditions for anti-inflammatory and antioxidant-based therapeutic interventions.

Author contributions

YP helped described this review and wrote the manuscript. YL helped with the literature search and revising the manuscript. YZ helped with the literature search. HW, JL, LH, HL, XX, LG, and XW helped revise the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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