

# Research Progress on Coping Strategies of Cognitive Impairment after Cardiac Surgery: A Systematic Review of Literature

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## ABSTRACT

Postoperative cognitive dysfunction (POCD) refers to a complication of neurological dysfunction after surgery, including one or more changes that are significantly lower than those before surgery.

The purpose of this study was to review the coping strategies and risk factors of POCD. Systemic research was conducted searching Pubmed, Web of Science, MEDLINE, and other websites with the keywords of cardiac surgery, cognitive impairment, and POCD.

Multiple factors have been associated with the treatment of POCD, including anesthetic, choice of analgesic drugs, anti-inflammatory drugs, erythropoietin, atherosclerosis, emotional factors, surgical, and other factors. Targeted treatments are carried out for risk factors that may affect POCD prevention, such as anesthetic drug prevention, anti-inflammatory drug prevention, and intraoperative prevention and other preventive measures are aimed at reducing the incidence of POCD after cardiac surgery.

## INTRODUCTION

With the progress of science and technology in recent years, the success rate of cardiac surgery, anesthesia technology, cardiopulmonary bypass technology and intensive care level are continuously improved, and the postoperative complications and mortality are continuously decreasing. Perioperative and in-hospital mortality decreased significantly to about 1-3%. Although effective brain protection strategies have been adopted, the incidence rate of postoperative neurological complications still is high, and POCD is one of them [Bruggemans 2013]. It is closely related to the decline of quality of life, increasing the economic burden of family and society. POCD refers to a complication of neurological dysfunction after surgery, including one or more changes that are significantly lower

than those before surgery. POCD is uniformly defined as "acute and persistent postoperative central nervous system (CNS) dysfunction" [Van Harten 2012]. The main manifestations are the decline of memory, attention, psychological reaction speed, social adaptability, and executive ability, and may even lead to permanent cognitive impairment. This is a problem that cannot be ignored for patients, families, and health systems [Hudetz 2009]. Postoperative delirium is a common, serious, under-recognized adverse event; it is associated with significant morbidity and mortality in elderly patients, leading to POCD in later stages. Delirium is an acute disorder with transient fluctuating disturbance of consciousness, attention, cognition, and perception, which in later stage is a strong predictor of POCD. While delirium may occur in every patient after surgery, the incidence is higher in the elderly patient. The occurrence of POCD also is a precursor of other complications and a predictor of possible death [Steinmetz 2009]. There are many factors that affect cognitive function after cardiac surgery. Similarly, there are many coping strategies for POCD, but there is no conclusion on its response. Prevention and treatment in different aspects can help prevent POCD and reduce the incidence rate of POCD. This paper looks for coping strategies by studying relevant literature in the last 20 years.

## METHOD

A systematic literature search was conducted using Pubmed and EMBASE, using the Mesh terms and keywords "POCD," "cardiac surgery," "cognitive impairment," "influencing factors," and "coping strategies" covering the past 20 years of articles through November 5, 2021. Investigators Bhushan Sandeep and Yifan Yan conducted the literature search, summarized the review articles, and prepared the first draft of the article, investigator Zongwei Xiao approved the final list of selected studies. Studies were retained for review after meeting strict inclusion criteria that included only prospective studies evaluating coping strategies for POCD in patients who had elective cardiac surgery. (Table 1)

## RESULTS

A total of 370 abstracts and titles were reviewed for potential eligibility. Based on the criteria for exclusion, 250

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abstracts were excluded. A total of 120 original articles were selected for further reading. Eighty studies were excluded after full reading for several reasons. (Figure 1) Forty articles were selected for inclusion in this systematic review. General anesthetic factors, choice of analgesic drugs, anti-inflammatory procedures, temperature and reheating process, blood pressure control, prevention of atrial fibrillation, hemoglobin level, and coagulation function, etc. were major coping factors for POCD prevention.

**Coping strategies – general anesthetic factors:** Propofol is a drug that has anti-inflammatory and inflammation delay effects [Sayed 2015]. The level of S-100β protein was positively correlated with nerve damage. Compared with desflurane anesthesia, the level of S100β in the propofol group was lower. Compared with fentanyl, propofol can significantly improve the nerve function of rats and reduce brain tissue damage. When the ischemic damage is relatively mild, propofol can continue to protect the nerves. The use of propofol is more beneficial to neuroprotection after cardiac surgery [Baki 2013]. Compared with full propofol intravenous anesthesia, sevoflurane inhalation anesthesia has improved cognition within one week after cardiac surgery, which may be related to better cognitive function [Schoen 2011]. The use of sevoflurane can improve short-term cognitive function [Bartels 2013]. After off-pump coronary artery bypass grafting, sevoflurane causes less arrhythmia than desflurane, but isoflurane can improve neurocognitive function after cardiac surgery [Hemmerling 2010]. Dexmedetomidine can act as a neuroprotective agent in ischemic and hypoxic areas and reduce the occurrence of POCD [Zhou 2016]. Ketamine has the potential to prevent neuroinflammation and POCD, reducing the incidence of POCD in the early (one week) after cardiac surgery [Tian 2018]. By reducing excitotoxic damage, regulating apoptotic proteins and interfering with inflammatory response, it reduces the damage of nerve cells after ischemia [Jin 2020]. Choosing the most suitable anesthetic can effectively reduce the occurrence of POCD and other cognitive problems.

**The choice of analgesic drugs:** Severe acute pain is related to POCD and analgesics can relieve pain. Meperidine is used as an analgesic after surgery, and its metabolite, norpethidine, is a central nervous system stimulant that can induce epilepsy and delirium. Meperidine is associated with an increased risk of delirium and POCD in elderly surgical patients, but current evidence does not show that other opioids (such as morphine, fentanyl, or hydromorphone) have significant differences in postoperative delirium or POCD [Fong 2006]. However, elderly patients who were given oral analgesics after surgery had a significantly lower risk of POCD [Wang 2014]. Choosing the right analgesic drugs can reduce the occurrence of POCD.

**Anti-inflammatory drugs:** Inflammation is the main mechanism leading to the occurrence of POCD after surgery. The application of anti-inflammatory drugs during surgery can weaken the occurrence and development of POCD to a certain extent [Riedel 2014]. Glucocorticoid drugs are a class of powerful anti-inflammatory drugs that can prevent

Table 1. Terms used in the systematic search for POCD in the present review

Database	Search terms
Pubmed	((("POCD" OR POCD[tiab]) AND (((("Cardiac Surgery"[Mesh] OR "Surgical Procedures, Operative" OR surgery[tiab])) OR ((("Diagnosis, Operative"[Mesh] OR "Anesthetic factors"[Mesh] OR postoperative[tiab] OR complication[tiab]))) AND ("Risk Factors"[Mesh] OR risk[tiab] OR Pathogenesis [tiab]) NOT Heart [tiab] NOT cardiac[tiab] NOT coronary[tiab]
Limits	Humans, English, Aged: 50+ years
Date of search	5 November 2021
Embase	pocd:ab,ti AND (risk* OR predict*:ab,ti) AND (surg* OR operat*:ab,ti) NOT cardiac:ab,ti NOT cardiovascular:ab,ti
Limits	Humans, English, Aged: 50+ years, Article, Article in press, Short Survey
Date of search	5 November 2021

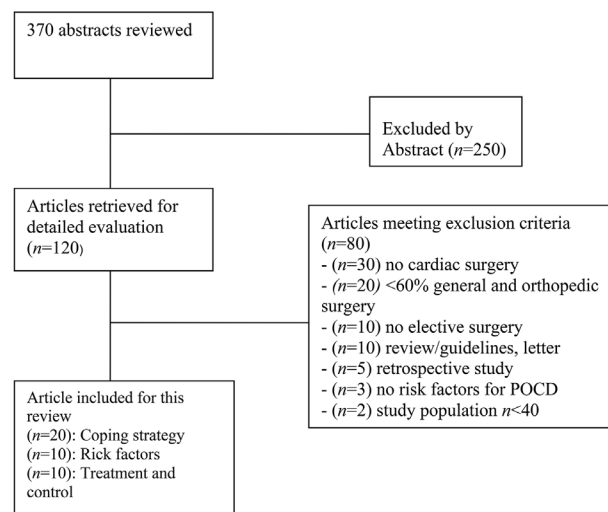


Figure 1. PRISMA diagram showing selection of articles for review of POCD.

the release of a variety of inflammatory mediators, inhibit the synthesis of cytokines, and reduce the generation of oxygen free radicals and their oxidative damage to tissue cells. During the perioperative period, application can effectively reduce the occurrence of postoperative complications. The anti-inflammatory effect of glucocorticoid therapy after CPB has been confirmed. At the same time, it also can improve the deterioration of kidney function, but it can cause infections caused by immunosuppression [Scrascia 2014]. The use of dexamethasone in the perioperative period can reduce the level of S100 calbindin, and on the other hand, it has been verified that dexamethasone can reduce the damage caused by inflammation [Glumac 2017]. Dexamethasone can prevent postoperative nausea and vomiting, improve analgesia, reduce opioid consumption, significantly reduce the incidence and

severity of sore throat and hoarseness after general anesthesia, and antagonize postoperative inflammation. Studies have found that high-dose and low-dose dexamethasone may lead to an increase in the incidence of early POCD, and high-dose dexamethasone should be used with caution in preventing the occurrence of POCD [Bhushan 2021]. Studies have found the neuroprotective effect of lidocaine. Lidocaine has been used for the potential protection of postoperative cognitive dysfunction in patients. Lidocaine has the functions of systemic anti-inflammatory, inhibiting the production of cytokines by microglia, and protecting the structure of mitochondria [Fang 2014].

**Erythropoietin:** Erythropoietin (epo) is a pleiotropic glycoprotein hormone that directly exerts neurotrophic and neuroprotective effects in the brain. Epo can protect cells from apoptosis, reduce inflammation, promote the proliferation and differentiation of pre-oligodendrocytes, and stimulate the production of growth factors, stimulate proliferation, migration, and differentiation to compensate for lost or damaged cells, and support functional reconstruction [Leng 2016]. Therefore, it can reduce the need for blood transfusion, reduce cerebral ischemia and excitotoxic injury, but in clinical applications, it has been found that it may increase the incidence of thromboembolism, and the risk will increase as the dose increases [Wehrle 2018]. The specific indications for use, dosage, and time still need further study.

**Atherosclerosis:** Aortic plaque is closely related to the occurrence of POCD [Bhushan 2021]. As the severity of atherosclerosis in the ascending aorta increases, neurological events and mortality significantly increase [Ostrowski 2018]. For coronary artery bypass graft patients with a history of stroke and transient ischemic attack, appropriate interventions can be selected to actively deal with plaque factors, such as carotid stenting or carotid endarterectomy [Gantner 2018]. Treat plaques in advance to prevent plaque rupture and reduce the occurrence of POCD.

**Intraoperative procedures:** Surgical procedures such as aortic cannulation, clamping of the aorta, and proximal bypass graft anastomosis can cause cerebral artery embolism [Evered 2010]. Clamping the aorta may cause the plaque in the aortic wall to rupture, form emboli with the blood flow, and embolize the cerebral artery. Extra-aortic ultrasound scanning is the most sensitive method for intraoperative detection of aortic atherosclerosis. Esophageal ultrasound can be used to avoid atherosclerotic plaques and prevent plaque rupture caused by clamping operations [Dávila-Román 1999]. When the cardiopulmonary bypass is opened, the impact force at the cannula is too large, which may cause damage to the vascular intima and form an embolus [Goto 2014]. The high-speed blood flow pattern generated at the CPB aortic cannulation hole may further cause the “sandblasting” effect and promote the rupture of atherosclerosis [Hogue 2006]. Arterial cannulation should choose a location with less plaque to avoid plaque rupture, leading to embolism.

**Temperature and reheating process:** Continuous hypothermia helps prevent POCD from heart surgery [Svenarud 2004]. During and after cardiopulmonary bypass, excessive brain temperature should be avoided to cause metabolic

dysfunction. Lowering the temperature can significantly reduce the brain's metabolic function. Avoiding excessive rewarming can reduce the incidence of POCD [Liu 2009]. Because each part of the brain does not heat up simultaneously during cardiopulmonary bypass, when the temperature rises too fast, the temperature difference between different brain tissues becomes more obvious, and there are obvious differences in metabolism, leading to ischemia and hypoxia in the brain tissue [Van Dijk 2002]. The rewarming process will impair the self-regulation function of the brain. Too fast or too high a rewarming speed will make the brain temperature too high, which can cause cognitive impairment [Hori 2015]. That is, a slower rewarming speed and a lower peak temperature will lead to significantly better cognitive performance after cardiac surgery. In low-risk populations undergoing coronary artery bypass surgery, intentionally sustained intraoperative and perioperative hypothermia and sustained normal body temperature are safe [Grigore 2002]. Hyperthermia can lead to a higher release of free radicals and excessive opening of the blood-brain barrier, further aggravating the damage of nerve cells. Among the neuroprotective factors, hypothermia is the only factor that reduces energy consumption, directly related to the maintenance of cell integrity, and can improve the tolerance of the brain and myocardium to the ischemic process [Joshi 2010]. The maintenance of hypothermia contributes to cognitive function from 3 weeks to 6 months after surgery [Boodhwani 2007].

**Blood pressure control:** Blood pressure regulation under cardiopulmonary bypass is another factor that affects POCD. It was found that during coronary artery bypass grafting, compared with the average intraoperative arterial pressure of 80-90mmHg, 60-70mmHg had a greater percentage of cognitive decline on the second day after surgery [Bhushan 2021]. Coronary artery bypass graft (CABG) patients maintain a mean arterial pressure (MAP) of 80 mmHg during CPB, and their morbidity and mortality are significantly lower than those who usually have a MAP of 50-60 mmHg. Maintaining a high level of MAP during CPB (close to the patient's own self-regulation range) can prevent hypoperfusion-related ischemia and improve prognosis. Higher MAP can improve cerebral perfusion pressure and improve collateral blood flow into the embolized blood vessel area, thereby reducing hypoperfusion injury [Hiraoka 2012]. Maintaining the average perfusion pressure at a physiological value (80-90 mmHg) during normal cardiopulmonary bypass is less associated with early POCD and delirium after coronary artery bypass surgery [Siepe 2011]. However, it is necessary to prevent postoperative blood pressure fluctuations and excessive high blood pressure, especially during the induction period of anesthesia and extubation, which will increase the risk of cerebrovascular rupture and hemorrhage [Charlson 2007]. Therefore, the blood pressure should be controlled within an appropriate range without too much fluctuation.

**Prevention of atrial fibrillation:** Atrial fibrillation has been shown to be an independent predictor of neurological events [Evered 2010]. Approximately 50% of patients undergoing cardiac surgery have atrial fibrillation, which is most likely to occur within 2-3 days after surgery [Wesselink 2015].

Perioperative atrial fibrillation and postoperative cognitive decline are positively correlated. The incidence of cognitive decline in patients with atrial fibrillation is significantly higher than that in patients without arrhythmia. It may be related to embolism caused by atrial fibrillation. Therefore, active prevention and management of atrial fibrillation can reduce the incidence of nerve damage [Van Dijk 2002]. Most patients with atrial fibrillation are treated with aspirin and/or warfarin, which can alleviate the effects of atrial fibrillation on neurological events [Evered 2010].

**Hemoglobin level:** During the past extracorporeal circulation, blood dilution must be performed to reduce blood viscosity and ensure microcirculation flow. This leads to a decrease in oxygen carrying capacity, which conflicts with the intention of ensuring microcirculation flow. In experimental low-temperature CPB, where the hematocrit level was high as 30%, the cerebral microcirculation blood flow was not impaired. There is a strong relationship between lower hematocrit levels and operative mortality [Hori 2015]. Extreme hemodilution (15-18% hematocrit) during CPB is associated with cognitive decline. Severe anemia during cardiopulmonary bypass may be related to POCD and should be avoided. The risks and potential benefits of blood transfusions should be carefully weighed [Fong 2006]. However, in these retrospective analyses, whether lower hematocrit is only a sign of other factors related to operative mortality or whether it is accidentally related, still needs further research.

**Cycle time:** When the cardiopulmonary bypass time is longer than 40 minutes, it obviously will affect the patient's cognitive function. The possible mechanism is that the longer the cardiopulmonary bypass time, the more serious the destruction of red blood cells, the lower the oxygen-carrying capacity of the blood, the massive activation of white blood cells, the release of inflammatory mediators, and the aggravation inflammatory reaction, the possibility of air and particle embolism during simultaneous infusion also is increased [Grigore 2002]. Therefore, shortening the operating time of extracorporeal circulation as much as possible can reduce the incidence of POCD [Goto 2014].

**Selection of circulation pipeline:** CABG patients with heparin-coated extracorporeal circulation circuit can significantly reduce the incidence of POCD. Compared with the non-heparin-coated extracorporeal circulation circuit, the level of C3a in the heparin-coated extracorporeal circulation circuit is significantly lower, and the reflected complement activation is significantly reduced. It may be related to the protective anti-inflammatory function of heparin during CPB [Joshi 2010]. Choosing the heparin layer of the circulation pipeline can reduce the occurrence of POCD.

**Carbon dioxide pretreatment circulating pipeline:** There may be air embolus in the CPB pipeline, which may lead to POCD. Therefore, carbon dioxide can be pre-filled in the cardiopulmonary bypass pipeline [Boodhwani 2007] in advance. Compared with air embolism, carbon dioxide embolism is more easily dissolved in the blood, which helps to reduce the formation of gas embolism. It can improve arterial capillary obstruction and brain injury. Experiments show that carbon dioxide can significantly reduce the number of

gas microemboli in the circulation [Hogue 2006]. However, it still is necessary to further confirm if it can effectively reduce the incidence rate of POCD.

**Ventilator related:** Hyperventilation caused by the ventilator during anesthesia can lead to severe hypocapnia, which is associated with a prolonged period of cognitive dysfunction, which lasts at least 3-6 days [Bhushan 2021]. The decline in cognitive function of patients after CABG is significantly related to the time of tracheal intubation. It may be that the inflammatory response caused by the patient's tube is involved in the change of postoperative cognitive function [Wang 2014]. Try to avoid excessive ventilation during the anesthesia and at the same time extubate the tube as early as possible to reduce the time for the ventilator to take the tube.

**Coagulation function:** After cardiac surgery, a large amount of thrombin, coagulation factors, platelets and other coagulation substances are consumed in a large amount in a short period of time, which leads to hyperfibrinolysis. Subsequently, due to the continuous increase of plasminogen activation inhibitory factor, fibrinolysis is inhibited and the body is in a hypercoagulable state that can lead to the occurrence of cerebral vascular microthromboembolism. The decline of coagulation function also will affect the change of postoperative cognitive function [Hiraoka 2012]. Therefore, a large amount of thrombin, clotting factors, platelets, etc. should be supplemented as soon as possible after cardiac surgery to prevent DIC.

**Blood recovery:** During heart surgery, blood in the surgical field needs to be recovered. At present, there are two methods of recovering blood, direct infusion of recovered blood without treatment (cardiotomy suction system) and blood recovered by centrifugation (cell protection) system). The cytoprotective system can reduce systemic inflammation and prevent fat emboli from being recovered, but the cytoprotective system may cause a large consumption of blood coagulation substances, leading to an increased risk of bleeding [Siepe 2011]. The use of cell protection systems can reduce the incidence of POCD [Svenarud 2004]. For the two methods of blood recovery, the pros and cons should be weighed and the appropriate method should be selected.

**Emotional factors:** Preoperative depression is significantly positively correlated with postoperative cognitive decline [Charlson 2007]. For patients undergoing heart valve replacement, preoperative negative emotions have a significantly higher incidence of POCD than preoperative positive emotions by [Wesselink 2015]. Depressed patients have more subjective complaints about their cognitive abilities than non-depressed patients [Kiviniemi 2018]. Through active preoperative education and emotional intervention, adjusting the patient's preoperative mood can help prevent many postoperative complications.

**Other factors:** For some diseases and drug factors related to POCD, such as preoperative hyperthyroidism, hypothyroidism, electrolyte imbalance, liver and kidney insufficiency, postoperative infection, sepsis, malnutrition, etc. [Kiviniemi 2018], anticholinergic drugs (such as atropine and scopolamine) or drugs with anticholinergic properties (such as tricyclic antidepressants and benzodiazepines), etc. [Wang 2014].



Actively deal with other diseases and adjust related drugs can effectively reduce the occurrence of POCD.

## CONCLUSION

POCD is one of the complications of cardiac surgery patients. The above coping strategies are summarized through the research progress of POCD prevention and treatment strategies, and targeted treatments are carried out for factors that may affect POCD, such as anesthetic drug prevention, anti-inflammatory drug prevention, and intraoperative prevention and other preventive measures. These measures are aimed at reducing the incidence of POCD after cardiac surgery, solving a major burden for patients and their families, society, and hospitals, and they are more conducive to the development of medical undertakings.

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