Review Article

Risk Factors Associated with Cognitive Decline after Cardiac Surgery: A Systematic Review

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Received 10 August 2015; Accepted 15 September 2015

Academic Editor: Koichi Hirata

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Modern day cardiac surgery evolved upon the advent of cardiopulmonary bypass machines (CPB) in the 1950s. Following this development, cardiac surgery in recent years has improved significantly. Despite such advances and the introduction of new technologies, neurological sequelae after cardiac surgery still exist. Ischaemic stroke, delirium, and cognitive impairment cause significant morbidity and mortality and unfortunately remain common complications. Postoperative cognitive decline (POCD) is believed to be associated with the presence of new ischaemic lesions originating from emboli entering the cerebral circulation during surgery. Cardiopulmonary bypass was thought to be the reason of POCD, but randomised controlled trials comparing with off-pump surgery show contradictory results. Attention has now turned to the growing evidence that perioperative risk factors, as well as patient-related risk factors, play an important role in early and late POCD. Clearly, identifying the mechanism of POCD is challenging. The purpose of this systematic review is to discuss the literature that has investigated patient and perioperative risk factors to better understand the magnitude of the risk factors associated with POCD after cardiac surgery.

1. Introduction

Neurological complication after cardiac surgery is of a considerable concern and debate exists as to which perioperative factors may be responsible for this adverse injury. Significant advances in all aspects of intraoperative and postoperative care mean cardiac surgery is now safer than ever before [1]. However, as the complexity of surgical procedures increases and the population ages, neurological manifestations and adverse cognitive outcomes are of concern. Cognitive decline limits the ability to complete activities of daily living [2] and increase the likelihood of dependence after discharge [3]. It is therefore paramount to determine the aetiology and extent of brain injury. Such complications vary from subtle cognitive impairment to catastrophic stroke events. The complexity of the brain is demonstrated by small lesions potentially causing significant loss of function, with larger lesions on occasion causing asymptomatic outcomes.

Over time, the demographic characteristics of patients undergoing cardiac surgery have shifted to include a higher proportion of elderly patients, undergoing increasingly complex procedures. The average age of cardiac surgery patients has increased from ~64 years in 2001 to ~67 years in 2010. The number of patients with neurological disease prior to surgery has nearly doubled from 1.4% in 2001 to ~2.8% in 2010. Cardiac surgery procedures have also become more complex, with the number of patients undergoing isolated coronary artery bypass graft (CABG) decreasing by almost 20% from 2001 to 2010. Despite higher patient risk profiles, the mortality rate has fallen slightly from 4.0% in 2001/2002 to 3.1% in 2010/2011 (National Cardiac Surgery Audit, UCL, 2012).

Routine clinical examination covers crucial neurological abnormalities such as ataxia, visual defects, paresis, and hypaesthesia [4]. It also includes focal neuropsychological deficits such as apraxia, dyscalculia, and aphasia. However,

more global cerebral dysfunction, such as neuropsychological decline, mood, and memory disturbances, personality changes, and decline in psychomotor speed are commonly missed because they require more explicit examination using specialised neuropsychological tests [5]. Postoperative cognitive decline (POCD) broadly refers to difficulties associated with memory and general information processing after surgery. At present POCD is not documented in the International Classification of Diseases and is not listed as a diagnosis.

2. Methods

2.1. Data Sources. A systematic literature search was conducted from searching articles from PubMed and EMBASE. Search terms were created by combining the following medical subject headings (MeSH terms): “Coronary Artery Bypass” OR “Coronary Artery Bypass, Off-Pump” OR “Valve Surgery” OR “Thoracic Surgery” OR “Cardiac Surgical Procedures” AND “Cognitive Therapy” OR “Cognition Disorders” OR “Cognition” OR “Neuropsychology” OR “Neuropsychological Tests” OR “Mild Cognitive Impairment.”

2.2. Study Selection. All studies published in English between June 1967 and August 2014 and featuring adult human subjects were eligible for review. Abstracts were excluded if they involved paediatric surgery, operations other than cardiac surgery, or no measurement of cognitive function. Case reports and studies of cardiac procedures such as angioplasty, angiography, valvuloplasty, and Transcatheter Aortic Valve Implantation (TAVI) were also excluded. Studies generating multiple publications from the same cohort were reported only once.

2.3. Quality Assessment. Abstracts involving both cardiac surgery and cognitive function were independently reviewed by two investigators (Nikil Patel and Emma M. L. Chung) and studies of adult cardiac surgery patients that assessed both before and after operative cognitive function were identified for full paper review. Where there was disagreement among investigators the full text was reviewed. Additionally, the reference lists of selected articles were evaluated for any additional articles of interest.

2.4. Analysis. Articles short-listed for full manuscript review were summarised in an Excel spreadsheet listing the study design (observational, RCT, etc.), number of patients, type(s) of surgery, outcome measures, and time point of neurocognitive assessment. Studies that included assessment of anxiety and depression were also recorded, as these conditions can impact the outcome of cognitive assessments. There was insufficient homogeneity between studies to allow a quantitative, meta-analytic approach of region of interest studies. Therefore, a critical, systematic review was undertaken.

3. Results

A total of 638 abstracts were systematically identified using our search criteria of which 426 papers were suitable for

full review. Of these, 296 were observational studies and 130 were RCTs. Although over 420 original research articles were identified as having investigated cognitive decline following cardiac surgery, we found little consensus on the incidence, severity, and time course of symptoms. Differing methodologies used between studies made it difficult to directly compare study findings through systematic meta-analysis.

3.1. Time of Postoperative Testing and Cognitive Decline. Most studies evaluating cognitive decline focus on changes in executive function, learning language, visual spatial skills, attention, and memory [6]. However, neuropsychological tests vary considerably between studies and also appear to depend on the timing of neurocognitive assessment. By narrowing the search to empirical research articles that studied postoperative neuropsychological assessment as a primary outcome, the number of publications was reduced to 137 articles. Thirty-three of these articles were excluded because the total percentage of patients who declined in cognitive tests was unclear. Four articles had published the same data twice and full-texts were unavailable for 6 articles. A total of 94 studies were identified to establish the distribution of cognitive decline over several time points. Grouping studies where assessments were performed at similar time points and plotting the proportion of patients estimated to be affected by cognitive decline suggest that 40–60% of patients experience cognitive decline when tested within 2 weeks of surgery, falling to 30–40% after 8–10 weeks, recovering to 10–20% at 1 year, with proportion of patients experiencing cognitive decline increasing again at 3–5 years, Figure 1.

Large variations in the estimated incidence of postoperative cognitive decline are observed, even after grouping studies where tests were performed at similar time points, Figure 1. Heterogeneity in assessment methods, patient demographics, and study design may be responsible for these variations.

3.2. Perioperative Risk Factors and Cognitive Decline. Further, we investigated perioperative risk factors associated with cognitive decline. Potential mechanisms implicated in the pathogenesis of cognitive decline investigated in previous research resulted in a total of 92 articles (see PRISMA chart in Supplementary Material available online at <http://dx.doi.org/10.1155/2015/370612>): anaesthesia: 15 studies; blood pressure: 5 studies; cerebral autoregulation: 4 studies; inflammatory responses: 26 studies; neuroprotective agents: 17 studies; hypothermia and rewarming: 19 studies and 6 studies, respectively.

3.3. Anaesthesia. Sedative and anaesthetic agents with *N*-methyl-*D*-aspartate receptor antagonist and γ -aminobutyric acid mediated properties can temporarily change the neurotransmission of the brain by interacting at a cellular level to achieve deep sedation during surgery [7]. Since it would be unethical to perform cardiac surgery without the use of anaesthetic agents, the impact of anaesthesia on cognition is difficult to study. Fifteen studies have investigated whether choice of anaesthesia impacts neurocognitive outcome after

FIGURE 1: Studies attempting to quantify neuropsychological decline at various time points. The weighted mean and standard deviation (number of patients and % decline) are plotted by combining data from a total of 15649 patients and 94 studies; discharge (17 studies), 1-2 weeks (16 studies), 1 month (4 studies), 6 weeks (15 studies), 2-3 months (18 studies), 6 months (11 studies), 1 year (8 studies), and 3-5 years (5 studies).

cardiac surgery. Of these, 8 were randomised controlled trials (RCTs), comparing 7 different types of anaesthetic agent. Studies showing an improvement, decline, and no difference in postoperative outcome are summarised in Table 1.

This research suggests that choice of anaesthetic has potential to affect cognition, particularly when tests are performed soon after surgery. However, in the majority of larger studies, the choice of anaesthetic had no impact on cognitive outcome.

3.4. Blood Pressure. A number of studies have investigated the association between low blood pressure during cardiac surgery and cognitive decline. Although normal blood pressure in conscious patients is approximately 120/80 mmHg, it is common for the blood pressure to be much lower during surgery. As the brain has a lower metabolic demand during anaesthesia, this is not thought to adversely affect tissue perfusion; however, low blood pressure may impair embolus clearance and affect the efficiency of cerebral autoregulation. A total of 5 studies have used neuropsychological tests to investigate whether mean arterial blood pressure had any impact on postoperative cognitive outcome, Table 2.

In the study by Gold et al., a higher mean arterial pressure (80–110 mmHg) during CPB appeared to be associated with a lower stroke rate (2.4%) compared to a low mean arterial pressure between 45 and 60 mmHg (7.2%), $p = 0.026$. However, at 6-month follow-up the proportion of patients with neuropsychological declines (11% and 12%, resp.) were comparable [8]. In another study, Siepe et al. showed greater proportion of patients with cognitive decline two days following CABG in patients with mean arterial pressure in the range 60–70 mmHg compared to 80–90 mmHg; however cerebral oxygen saturation was similar in both groups [9]. The largest RCT by Charlson et al. found no difference in

cognition between a “custom” group (average BP: 79 mmHg) and High BP group (average BP: 89 mmHg); however, the average difference in BP between groups was only 10 mmHg, which may not be a clinically significant difference [10]. Overall, studies appear to support the idea that maintenance of a sufficiently high mean arterial pressure during cardiac surgery is important for safeguarding perfusion to the brain.

3.5. Cerebral Autoregulation. Some researchers have proposed that it is not mean arterial pressure (MAP) *per se* that contributes to cognitive decline, but the capacity of the brain's blood flow regulation mechanisms to respond appropriately to blood pressure variations and changes in oxygen saturation. A number of studies have investigated cerebral autoregulation (CA) in response to blood pressure changes during cardiac surgery and found that a significant proportion of patients struggle to autoregulate their cerebral blood supplies intraoperatively [11]. However, only 4 studies have specifically investigated CA during cardiac surgery in conjunction with pre- and postoperative neuropsychological assessment, Table 3.

All four studies determined pressure-flow and metabolic-flow cerebral autoregulation during cardiopulmonary bypass using the ^{133}Xe clearance cerebral blood flow method. Two studies in Table 3 by the same author (Patel et al.) support the theory that impaired cerebral autoregulation is associated with a decline in postoperative outcome at 6 weeks, whereas two studies showed no association. The largest study by Newman et al. investigated CA in 215 patients and concluded that neuropsychological dysfunction at discharge was not explained by impaired CA; however increased oxygen extraction (measured using a thermodilution pulmonary artery catheter) was observed to be associated with a decline in some cognitive tests. They interpreted this suggesting that an imbalance in cerebral tissue oxygen supply may contribute to POCD [12]. In a recent trial it has also been proposed that some anaesthetic agents suppress autoregulatory responses more than others [13]. As far as we are aware, no studies have yet looked at the relationship between CA and POCD beyond 6 weeks.

3.6. Inflammatory Responses. All types of surgery have the risk of developing systemic inflammation; however, in cardiac surgery using CPB the blood is exposed to foreign surfaces which have potential to stimulate proinflammatory responses. Inflammation causes endothelial dysfunction, which can lead to leakage between the blood-brain barrier and tissue oedema [14]. It has been shown that cytokines (e.g., TNF-alpha, interleukin-1, and interleukin-6) have been linked to neuropathology [15, 16]. These elementary changes are hypothesised to affect the brain regardless of microembolic load received during surgery [17, 18] and potentially provide an explanation for early cognitive decline [19].

Cardiopulmonary bypass components that come into contact with the blood can be coated with biocompatible materials such as poly-2-methoxyethylacrylate, heparin, trillium, and synthetic proteins. These coatings aim to reduce inflammatory responses triggered during CPB.

TABLE 1: Studies comparing cognition after cardiac surgery following administration of different types of anaesthetic.

Study	Study design	Number of patients	Type of anaesthesia/drug	Time of assessment	Outcome
Dumas et al., 1999 [37]	RCT	48	Fentanyl and early extubation	8 weeks	Improved cognition
Dowd et al., 2001 [38]	RCT	78	Propofol and lorazepam	6–12 months	Improved cognition
Bottio et al., 2007 [39]	Obsv.	50	Epidural anaes.	6 months	Improved cognition
Delphin et al., 2007 [40]	Obsv.	91	Sevoflurane and isoflurane	2 hours and 1 day	Improved cognition
Kanbak et al., 2007 [41]	RCT	40	Isoflurane, sevoflurane, and desflurane	3 and 6 days	Improved cognition
Hudetz et al., 2009 [42]	Obsv.	78	Ketamine	1 week	Improved cognition
Schoen et al., 2011 [43]	RCT	117	Sevoflurane and propofol	2, 4, and 6 days	Improved cognition
Kanbak et al., 2007 [41]	RCT	40	Sevoflurane and desflurane	3 and 6 days	Decline
Kadoi et al., 2003 [44]	RCT	180	Propofol and fentanyl	6 months	No difference
Silbert et al., 2006 [45]	Obsv.	300	Fentanyl	1 week, 3 months, 1 year	No difference
Kadoi and Goto, 2007 [46]	Obsv.	109	Sevoflurane	6 months	No difference
Lehmann et al., 2007 [47]	RCT	66	Sufentanil and midazolam	Discharge	No difference
Evered et al., 2011 [48]	Obsv.	281	General anaesthetics	1 week and 3 months	No difference
Parra et al., 2011 [49]	Obsv.	48	Sevoflurane	3 months	No difference
Royse et al., 2011 [50]	RCT	180	Desflurane and propofol	Discharge and 3 months	No difference

Obsv.: observational.

TABLE 2: Studies investigating POCD associated with intraoperative blood pressure variation.

Study	Study design	Number of patients	Type of intervention	Time of assessment	Outcome
Gold et al., 1995 [8]	RCT	248	High (80–100 mmHg) versus low (50–60 mmHg) BP	6 months	Decline with lower BP
Siepe et al., 2011 [9]	RCT	92	High (80–90 mmHg) versus low (60–70 mmHg) BP	2 days	Decline with lower BP
Gottesman et al., 2007 [51]	Obsv.	15	Low MAP (50–70 mmHg)	3–5 days and 1 month	Decline with lower BP
Newman et al., 1995 [52]	Obsv.	237	Low MAP (50–60 mmHg)	Discharge	Decline with lower BP
Charlson et al., 2007 [10]	RCT	412	High MAP (57–90 mmHg) versus custom (capped at 90 mmHg)	6 months	No difference in outcome

Obsv.: observational.

TABLE 3: Studies investigating cerebral autoregulation during cardiac surgery in conjunction with neurocognitive tests.

Study	Study design	Number of patients	Cerebral autoregulation measures	Time of assessment	Outcome
Patel et al., 1993 [53]	RCT	70	Xenon-133 isotope clearance, CMRO ₂ (cerebral metabolic rate for oxygen), CERO ₂ (cerebral extraction ratio for oxygen)	6 weeks	Decline with impaired CA
Patel et al., 1996 [54]	RCT	70	CBF, CBFv, and O ₂ saturation were measured during 4 phases of surgery	6 weeks	Decline with impaired CA
Govier et al., 1984 [55]	Obsv.	67	Partial pressure of arterial carbon dioxide (PaCO ₂), clearance of xenon-133	Discharge	No difference
Newman et al., 1994 [12]	Obsv.	215	Xenon-133 clearance, CMRO ₂ , cerebral AV difference (C[AV]O ₂)	Discharge	No difference

Obsv.: observational.

TABLE 4: Studies investigating whether biomarkers associated with inflammation and/or interventions aimed at reducing inflammation are associated with changes in cognition after surgery.

Study	Study design	Number of patients	Marker for cerebral damage	Time of assessment	Outcome
Fitch et al., 1999 [20]	RCT	35	Inhibition of complement activation by specific antibody and no antibody	Discharge	Improved cognition
Heyer et al., 2002 [21]	RCT	99	Inhibition of complement activation by heparin-coated CPB	5 days and 6 weeks	Improved cognition
Baufreton et al., 2005 [19]	RCT	30	Inhibition of complement activation by heparin-coated CPB	Discharge	Improved cognition
Skrabal et al., 2006 [22]	RCT	39	PMEA-coated circuits and noncoated circuits	7–10 days	Improved cognition
Wimmer-Greinecker et al., 1998 [56]	Obsv.	76	>S-100 and NSE	5 days and 2 months	Decline
Jönsson et al., 1999 [57]	Obsv.	132	>S-100	2 weeks and 2 months	Decline
Kilminster et al., 1999 [58]	Obsv.	130	>S-100	6–8 weeks	Decline
Rasmussen et al., 1999 [59]	Obsv.	35	>NSE	Discharge and 3 months	Decline
Derkach et al., 2000 [60]	RCT	27	>S-100 and NSE (deep and mild hypothermic)	6 months	Decline
Diegeler et al., 2000 [61]	RCT	40	>S-100 (on- and off-pump)	1 week	Decline
Georgiadis et al., 2000 [62]	Obsv.	190	>S-100	Discharge	Decline
Lloyd et al., 2000 [63]	RCT	125	>S-100 (on- and off-pump)	3 months	Decline
Basile et al., 2001 [64]	Obsv.	16	>S-100 and NSE	6 months	Decline
Rasmussen et al., 2002 [65]	Obsv.	15	>NSE	Discharge and 3 months	Decline
Farsak et al., 2003 [66]	Obsv.	50	>S-100	Discharge	Decline
Mathew et al., 2003 [67]	Obsv.	460	Reduced preoperative endotoxin immunity	6 weeks	Decline
Jönsson et al., 2004 [68]	Obsv.	56	>S-100	6 months	Decline
Kofke et al., 2004 [69]	Obsv.	28	Apo epsilon 4 allele, >S-100	8 and 24 hrs	Decline
Snyder-Ramos et al., 2004 [70]	Obsv.	64	>S-100 and NSE	Throughout 7 days	Decline
Kálmán et al., 2006 [71]	Obsv.	14	>Cytokine interleukin-6	1 week and 6 months	Decline
Ramlawi et al., 2006 [72]	Obsv.	42	>C-reactive protein	6 hours and 4 days	Decline
Lazibat et al., 2012 [24]	Obsv.	62	>S-100	2 days	Decline
Bayram et al., 2013 [25]	Obsv.	64	>S-100	1 week	Decline
Westaby et al., 2001 [26]	Obsv.	1001	>S-100 and NSE	5 days and 3 months	No difference
Mathew et al., 2005 [73]	Obsv.	440	Statin treatment	6 weeks	No difference
Plaschke et al., 2013 [74]	Obsv.	151	Preoperative serum anticholinergic activity	3 months	No difference

NSE: neuron-specific enolase, PMEA: poly-2-methoxyethylacrylate, and Obsv.: observational.

Heparin-coated circuits, in particular, have undergone considerable investigation in previous research. A total of 26 studies (including 7 RCTs) have used neuropsychological tests to investigate whether there is a strong association between inflammation and cognitive decline, Table 4.

All studies that have randomised patients to receive a heparin-coated CPB system found neuropsychological outcome was better in patients receiving the heparin-coated circuit [19–22]. In studies investigating inflammatory responses,

a consensus panel has concluded that “*the use of surface-modified circuits might be effective at attenuating the systemic inflammatory response to CPB and improving outcome*” [23]. Many markers associated with susceptibility to brain ischaemia such as S-100 beta and neuron-specific enolase (NSE) have been suggested to be associated with an increased risk of cognitive decline [24–26]. Inflammation may also play an important role in our understanding of long-term cognitive function. Biomarkers for inflammation tend to be

TABLE 5: RCTs investigating the efficacy of neuroprotection, or neuroprotective agents, in reducing cognitive decline after cardiac surgery.

Study	Number of patients	Type of neuroprotective drug	Time of assessment	Outcome
Grieco et al., 1996 [75]	29	GM-100 (ganglioside) or placebo	1 week and 6 months	Improved cognition
Arrowsmith et al., 1998 [76]	171	Remacemide or placebo	2 months	Improved cognition
Svensson et al., 2002 [77]	403	Mannitol, thiopental, MgSO ₄ , lidocaine	2-3 weeks	Improved cognition
Wang et al., 2002 [29]	118	Lidocaine or placebo	9 days	Improved cognition
Uebelhack et al., 2003 [78]	64	Piracetam or placebo	3 days	Improved cognition
Szalma et al., 2006 [79]	98	Piracetam or placebo	6 weeks	Improved cognition
Haljan et al., 2009 [80]	32	Erythropoietin or placebo	Discharge and 2 months	Improved cognition
Hudetz et al., 2009 [42]	52	Ketamine or placebo	1 week	Improved cognition
Zhang et al., 2011 [81]	200	Benzyl alcohols or saline (placebo)	Discharge and 3 months	Improved cognition
Kong et al., 2002 [82]	245	Chlormethiazole/administration or placebo	4-7 weeks	No difference
Taggart et al., 2003 [83]	150	Imidazoles: low dose (10 mg) or high dose (100 mg) or placebo	5 days and 3 months	No difference
Mathew et al., 2004 [84]	914	Pexelizumab bolus, bolus plus infusion, or placebo	4 days and 1 month	No difference
Mathew et al., 2005 [73]	440	Hydroxymethylglutaryl-CoA reductase inhibitors	6 weeks	No difference
Hogue et al., 2007 [85]	174	17-beta estradiol or placebo	4-6 weeks	No difference
Mathew et al., 2009 [31]	241	Lidocaine or placebo	6 weeks and 1 year	No difference
Mitchell et al., 2009 [32]	158	Lidocaine or placebo	10 weeks and 25 weeks	No difference
Holinski et al., 2011 [86]	88	Piracetam or placebo	3 days	No difference

higher in patients with chronic cardiovascular disease [25]. Overall, the role of inflammation in the pathogenesis of cognitive decline appears to warrant further investigation [27].

3.7. Neuroprotective Agents. A number of neuroprotective agents have been investigated to assess whether these could be administered to help preserve neurocognitive function. The results of 17 studies investigating whether neuroprotective agents reduce the incidence of POCD are summarised in Table 5.

One of the most commonly used neuroprotective agents is Lidocaine, which featured in 4 of the 17 studies. Lidocaine is thought to inhibit inflammatory responses during cardiac surgery by modulation of inflammatory mediators, reduction in cerebral metabolism, and deceleration of ischaemic ion fluxes [28]. Two studies showed improved outcome with the use of the drug [29, 30], while two studies showed no difference [31, 32]. Currently, no trials have demonstrated a reproducible clinically significant benefit conferred by the use of any particular neuroprotective drug.

3.8. Hypothermia and Rewarming. The patient's temperature during cardiac surgery has long been thought to play a role in neurological outcome. Several studies have focused their trials on whether reducing the metabolic demand of the brain through hypothermia is neuroprotective. Based on our literature search, 41 studies investigating the effects of temperature were identified. Seventeen studies were excluded

from the final result due to lack of clarity in neuropsychological assessments and outcomes. Results from a total of 19 studies investigating the effect of temperature on pre- and postoperative neuropsychological tests are summarised in Table 6.

Some studies suggest that hypothermia is more effective than normothermia in protecting the brain during surgery; however, other studies report no obvious difference between "mild hypothermia" and "normothermia" in terms of neuropsychological performance at discharge (49% and 45%, resp.) and at 3 months (4% and 8%, resp.) [33].

Some researchers have proposed that the brain could be susceptible to insult during rewarming from hypothermia, particularly if cerebral autoregulation mechanisms are unable to compensate for a sudden increase in metabolic activity associated with changes in temperature. Six studies have been conducted to examine the effect of rewarming rate on POCD, and all of these have shown a benefit in postoperative outcome associated with slower rewarming, Table 7.

4. Conclusion

Neuropsychological function is a soft outcome measure and has proved challenging to quantify postoperatively. Although neuropsychological tests theoretically provide a highly sensitive means of quantifying changes in cognition, differences in test batteries, timing of assessment, and criteria for defining neuropsychological decline generate considerable heterogeneity in the data, which limits our ability to compare

TABLE 6: Studies investigating POCD associated with temperature during cardiac surgery.

Study	Study design	Number of patients	Mean temperature (Celsius)	Time of assessment	Outcome
Grimm et al., 2000 [87]	RCT	144	(1) Normothermia: 37°C (2) Hypothermia: 32°C	1 week and 4 months	Improved cognition (with normothermia)
Shaaban-Ali et al., 2002 [88]	RCT	60	(1) Normothermia: 34°C (2) Hypothermia: 28°C	5 days	Improved cognition (with normothermia)
Nathan et al., 1995 [89]	Obsv.	30	Maintain $\leq 34^\circ\text{C}$	1 week	Improved cognition (with hypothermia)
Grocott et al., 2002 [90]	Obsv.	300	Post-op hypothermia only	6 weeks	Improved cognition (with hypothermia)
Kadoi et al., 2004 [91]	RCT	60	(1) Normothermia: 37°C (2) Hypothermia: 32°C	1 month	Improved cognition (with hypothermia)
Boodhwani et al., 2006 [92]	RCT	448	(1) Normothermia: 37°C (2) Hypothermia: 34°C	1 week	Improved cognition (with hypothermia)
Hiraoka et al., 2012 [93]	Obsv.	11	Hypothermia: 20–22°C	3 weeks and 6 months	Improved cognition (with hypothermia)
McLean et al., 1994 [94]	RCT	155	(1) Hyperthermia: $>34^\circ\text{C}$ (2) Hypothermia: $<28^\circ\text{C}$	5 days and 3 months	No difference
Regragui et al., 1996 [95]	RCT	97	(1) Normothermia: 37°C (2) Hypothermia: 28°C & 32°C	6 weeks	No difference
Heyer et al., 1997 [96]	RCT	99	(1) Normothermia: 34°C (2) Hypothermia: 28°C	Discharge and 6 weeks	No difference
Kneebone et al., 1998 [97]	Obsv.	50	(1) Normothermia: 37°C (2) Hypothermia: 30–32°C	1 week	No difference
Reich et al., 1999 [98]	Obsv.	149	(1) Deep hypothermia: 12–15°C (<25 mins) (2) Deep hypothermia: 12–15°C (>25 mins)	1 month	No difference
Kaukinen et al., 2000 [99]	RCT	36	(1) Normothermia: 36–37°C (2) Hypothermia: 28°C	5 days and 11–23 months	No difference
Górna et al., 2001 [100]	Obsv.	33	No full text	3–10 days	No difference
Grigore et al., 2001 [101]	RCT	300	(1) Normothermia: 35.5–36.5°C (2) Hypothermia: 28–30°C	6 weeks	No difference
Kaukuntla et al., 2004 [102]	Obsv.	60	(1) Normothermia: 35°C (2) Differential temperature management	1 and 8 weeks	No difference
Reich et al., 2004 [103]	Obsv.	61	Monitoring during deep hypothermic arrest (28°C)	Discharge	No difference
Boodhwani et al., 2007 [33]	RCT	268	(1) Normothermia: 37°C (2) Hypothermia: 34°C	Discharge and 3 months	No difference
Kunihara et al., 2007 [104]	Obsv.	26	(1) Normothermia: 34°C (2) Hypothermia: 22°C	1 week	No difference

Obsv.: observational.

the results of different studies. Depending on the timing of the neurocognitive tests and the definition used for determining decline, the reported incidence of neurocognitive decline after cardiac surgery varied extensively. The outcome suggests that 50–70% of patients experience cognitive decline when tested within one week of surgery, falling to 30–50% after 8–10 weeks, recovering to 10–20% at 1 year, and then declines again at 3–5 years. Currently, there is no widely accepted clinical definition of cognitive decline; therefore, it is possible that arbitrary definitions of decline have resulted in an

overestimation of the incidence of decline. At present, there is no evidence to suggest that the long-term incidence of cognitive decline differs from that of nonoperative controls. Estimating long-term cognitive decline can be difficult, as normal ageing and dementia interfere with studies with older populations.

Further research is required to develop a more dynamic and nuanced picture of interactions between underlying pre- and perioperative risk factors. It is apparent that studies investigating isolated perioperative factors are insufficient to

TABLE 7: Studies investigating POCD associated with the rate of rewarming during cardiac surgery.

Study	Study design	Number of patients	Mean temperature (Celsius)	Time of assessment	Outcome
Mora et al., 1996 [105]	RCT	138	(1) Rewarm 1-2°C (per increase) (2) Rewarm 3-5°C (per increase)	1-3 days, 7-10 days, and 1 month	Improved cognition with slower rewarm
Nathan et al., 2001 [106]	Obsv.	294	(1) Rewarm to 34°C (1°C per increase) (2) Rewarm to 37°C (3°C per increase)	1 week and 3 months	Improved cognition with slower rewarm
Grigore et al., 2002 [107]	Obsv.	100	(1) Rewarm to 32°C (max within 3 mins) (2) Rewarm to 37°C (max within 3 mins)	6 weeks	Improved cognition with slower rewarm
Kawahara et al., 2003 [108]	RCT	100	(1) Rewarm 1-2°C (per increase) (2) Rewarm 4-5°C (per increase)	1 month	Improved cognition with slower rewarm
Nathan et al., 2007 [109]	RCT	223	(1) Rewarm to 34°C (1°C per increase) (2) Rewarm to 37°C (3°C per increase)	1 week	Improved cognition with slower rewarm
Sahu et al., 2009 [110]	RCT	80	(1) Rewarm 1-3°C (per increase) (2) Rewarm 3-5°C (per increase)	5 days	Improved cognition with slower rewarm

Obsv.: observational.

explain complex interactions between temperature, cerebral autoregulation, oxygen saturation, and brain metabolism. To date, isolated interventions and neuroprotective drugs aimed at improving cognitive outcome have proved to be largely ineffective. Literature examining underlying and perioperative risk factors associated with the pathogenesis of cognitive decline suggests that there is no single causative factor responsible for POCD. It seems likely that the causes are multifactorial, due to emboli, impaired perfusion, chronic cardiovascular disease, and inflammatory responses.

Interpreting the risk factors associated with postoperative cognitive decline, it seems that efforts to protect the brain during surgery are intrinsically linked with the need to control the progression of cardiovascular disease, especially in older patients. It is possible that patients may be exceeding a “threshold” of preexisting vulnerability where the brain's ability to compensate for injuries or inflammation during surgery is absent. It is also important to address that cardiac surgery equipment advances are a confounder within this review and should be considered. In summary, the literature examining underlying risk factors and perioperative risk factors associated with the pathogenesis of cognitive decline suggests that there is no single factor responsible for postoperative cognitive decline or single intervention capable of protecting the brain during surgery. Overall, the pathogenesis of cognitive decline following surgery still remains unclear.

Several factors have been associated with brain injury including hypoperfusion, arrhythmias, rapid rewarming, and inflammation (local or global) [34–36]. The process of preventing such brain injury involves prevention of such events occurring; however, to date no single intervention has successfully prevented cognitive decline, signalling an increased likelihood of a multifactorial aetiology. The advent of new technologies to prevent physiological stress on the brain has focussed on neuroprotective agents or perfusionist strategies. Although prevention has an important role, it would be ideal to develop methods of protecting or restoring neurocognitive decline to nearer preoperative baselines.

Cardiac surgery is a triumph of modern day medicine, and its acceptance as a safe procedure is widespread. Unfortunately, postoperative cognitive issues remain a consideration. As cardiac surgery procedures are now being challenged by less invasive methods, perhaps intraoperative transcranial Doppler monitoring, neuropsychological tests, and neuroimaging will play an increasingly important role in optimising treatment.

Conflict of Interests

The authors declare that they have no conflict of interests.

Authors' Contribution

Nikil Patel and Emma M. L. Chung conducted the literature search and data extraction. Nikil Patel, Emma M. L. Chung, and Jatinder S. Minhas drafted the paper.

Acknowledgments

The authors would like to thank the Department of Cardiovascular Sciences, University of Leicester, and the Department of Medical Physics, University Hospitals of Leicester NHS Trust. Nikil Patel is funded by the National Institute of Health Research (NIHR) Leicester Cardiovascular Biomedical Research Unit. Jatinder S. Minhas is an Academic Clinical Fellow in Stroke Medicine funded by the NIHR.

References

- [1] O. A. Selnes, G. M. McKhann, L. M. Borowicz Jr., and M. A. Grega, “Cognitive and neurobehavioral dysfunction after cardiac bypass procedures,” *Neurologic Clinics*, vol. 24, no. 1, pp. 133–145, 2006.
- [2] B. Phillips-Bute, J. P. Mathew, J. A. Blumenthal et al., “Association of neurocognitive function and quality of life 1 year after

- Coronary Artery Bypass Graft (CABG) surgery," *Psychosomatic Medicine*, vol. 68, no. 3, pp. 369–375, 2006.
- [3] J. Steinmetz, K. B. Christensen, T. Lund, N. Lohse, and L. S. Rasmussen, "Long-term consequences of postoperative cognitive dysfunction," *Anesthesiology*, vol. 110, no. 3, pp. 548–555, 2009.
 - [4] T. Brott, H. P. Adams Jr., C. P. Olinger et al., "Measurements of acute cerebral infarction: a clinical examination scale," *Stroke*, vol. 20, no. 7, pp. 864–870, 1989.
 - [5] J. M. Murkin, S. P. Newman, D. A. Stump, and J. A. Blumenthal, "Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery," *Annals of Thoracic Surgery*, vol. 59, no. 5, pp. 1289–1295, 1995.
 - [6] J. L. Rudolph, K. A. Schreiber, D. J. Culley et al., "Measurement of post-operative cognitive dysfunction after cardiac surgery: a systematic review," *Acta Anaesthesiologica Scandinavica*, vol. 54, no. 6, pp. 663–677, 2010.
 - [7] R. G. Eckenhooff, J. S. Johansson, H. Wei et al., "Inhaled anesthetic enhancement of amyloid-beta oligomerization and cytotoxicity," *Anesthesiology*, vol. 101, no. 3, pp. 703–709, 2004.
 - [8] J. P. Gold, M. E. Charlson, P. Williams-Russo et al., "Improvement of outcomes after coronary artery bypass: a randomized trial comparing intraoperative high versus low mean arterial pressure," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 110, no. 5, pp. 1302–1314, 1995.
 - [9] M. Siepe, T. Pfeiffer, A. Gieringer et al., "Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium," *European Journal of Cardio-Thoracic Surgery*, vol. 40, no. 1, pp. 200–207, 2011.
 - [10] M. E. Charlson, J. C. Peterson, K. H. Krieger et al., "Improvement of outcomes after coronary artery bypass II: a randomized trial comparing intraoperative high versus customized mean arterial pressure," *Journal of Cardiac Surgery*, vol. 22, no. 6, pp. 465–472, 2007.
 - [11] M. Ono, B. Joshi, K. Brady et al., "Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke," *British Journal of Anaesthesia*, vol. 109, no. 3, pp. 391–398, 2012.
 - [12] M. F. Newman, N. D. Croughwell, J. A. Blumenthal et al., "Effect of aging on cerebral autoregulation during cardiopulmonary bypass. Association with postoperative cognitive dysfunction," *Circulation*, vol. 90, no. 5, pp. II243–II249, 1994.
 - [13] T. Tanaka, S. Kai, T. Koyama et al., "General anesthetics inhibit erythropoietin induction under hypoxic conditions in the mouse brain," *PLoS ONE*, vol. 6, no. 12, Article ID e29378, 2011.
 - [14] N. J. Abbott, "Inflammatory mediators and modulation of blood-brain barrier permeability," *Cellular and Molecular Neurobiology*, vol. 20, no. 2, pp. 131–147, 2000.
 - [15] N. Terrando, L. I. Eriksson, J. Kyu Ryu et al., "Resolving post-operative neuroinflammation and cognitive decline," *Annals of Neurology*, vol. 70, no. 6, pp. 986–995, 2011.
 - [16] M. Cibelli, A. R. Fidalgo, N. Terrando et al., "Role of interleukin-1 β in postoperative cognitive dysfunction," *Annals of Neurology*, vol. 68, no. 3, pp. 360–368, 2010.
 - [17] B. Reinsfelt, S.-E. Ricksten, H. Zetterberg, K. Blennow, J. Fredén-Lindqvist, and A. Westerlind, "Cerebrospinal fluid markers of brain injury, inflammation, and blood-brain barrier dysfunction in cardiac surgery," *Annals of Thoracic Surgery*, vol. 94, no. 2, pp. 549–555, 2012.
 - [18] B. Reinsfelt, A. Westerlind, K. Blennow, H. Zetterberg, and S.-E. Ricksten, "Open-heart surgery increases cerebrospinal fluid levels of Alzheimer-associated amyloid β ," *Acta Anaesthesiologica Scandinavica*, vol. 57, no. 1, pp. 82–88, 2013.
 - [19] C. Baufreron, P. Allain, A. Chevailler et al., "Brain injury and neuropsychological outcome after coronary artery surgery are affected by complement activation," *Annals of Thoracic Surgery*, vol. 79, no. 5, pp. 1597–1605, 2005.
 - [20] J. C. K. Fitch, S. Rollins, L. Matis et al., "Pharmacology and biological efficacy of a recombinant, humanized, single-chain antibody C5 complement inhibitor in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass," *Circulation*, vol. 100, no. 25, pp. 2499–2506, 1999.
 - [21] E. J. Heyer, K. S. Lee, H. E. Manspeizer et al., "Heparin-bonded cardiopulmonary bypass circuits reduce cognitive dysfunction," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 16, no. 1, pp. 37–42, 2002.
 - [22] C. A. Skrabal, A. Khosravi, B. Westphal, G. Steinhoff, and A. Liebold, "Effects of poly-2-methoxyethylacrylate (PMEA)-coating on CPB circuits," *Scandinavian Cardiovascular Journal*, vol. 40, no. 4, pp. 224–229, 2006.
 - [23] K. G. Shann, D. S. Likosky, J. M. Murkin et al., "An evidence-based review of the practice of cardiopulmonary bypass in adults: a focus on neurologic injury, glycemic control, hemodilution, and the inflammatory response," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 132, no. 2, pp. 283–290.e3, 2006.
 - [24] I. Lazibat, Ž. Sutlić, K. Brkić, B. Nevajda, J. Šikić, and A. H. Meštrović, "Predictors of short-term neurocognitive outcome following coronary revascularisation (CABG) depending on the use of cardiopulmonary bypass," *Collegium Antropologicum*, vol. 36, no. 3, pp. 827–833, 2012.
 - [25] H. Bayram, M. Hidiröglü, L. Cetin et al., "Comparing S-100 beta protein levels and neurocognitive functions between patients undergoing on-pump and off-pump coronary artery bypass grafting," *Journal of Surgical Research*, vol. 182, no. 2, pp. 198–202, 2013.
 - [26] S. Westaby, K. Saatvedt, S. White, T. Katsumata, W. van Oeveren, and P. W. Halligan, "Is there a relationship between cognitive dysfunction and systemic inflammatory response after cardiopulmonary bypass?" *Annals of Thoracic Surgery*, vol. 71, no. 2, pp. 667–672, 2001.
 - [27] D. Carnevale, G. Mascio, M. A. Ajmone-Cat et al., "Role of neuroinflammation in hypertension-induced brain amyloid pathology," *Neurobiology of Aging*, vol. 33, no. 1, pp. 205.e19–205.e29, 2012.
 - [28] S. Mitchell and D. Gorman, "The pathophysiology of cerebral arterial gas embolism," *The Journal of Extra-Corporeal Technology*, vol. 34, no. 1, pp. 18–23, 2002.
 - [29] D. Wang, X. Wu, J. Li, F. Xiao, X. Liu, and M. Meng, "The effect of lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery," *Anesthesia and Analgesia*, vol. 95, no. 5, pp. 1134–1141, 2002.
 - [30] L. G. Svensson, E. M. Nadolny, D. L. Penney et al., "Prospective randomized neurocognitive and S-100 study of hypothermic circulatory arrest, retrograde brain perfusion, and antegrade brain perfusion for aortic arch operations," *Annals of Thoracic Surgery*, vol. 71, no. 6, pp. 1905–1912, 2001.
 - [31] J. P. Mathew, G. B. Mackensen, B. Phillips-Bute et al., "Randomized, double-blinded, placebo controlled study of neuroprotection with lidocaine in cardiac surgery," *Stroke*, vol. 40, no. 3, pp. 880–887, 2009.

- [32] S. J. Mitchell, A. F. Merry, C. Frampton et al., "Cerebral protection by lidocaine during cardiac operations: a follow-up study," *Annals of Thoracic Surgery*, vol. 87, no. 3, pp. 820–825, 2009.
- [33] M. Boodhwani, F. Rubens, D. Wozny, R. Rodriguez, and H. J. Nathan, "Effects of sustained mild hypothermia on neurocognitive function after coronary artery bypass surgery: a randomized, double-blind study," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 134, no. 6, pp. 1443–1452.e1, 2007.
- [34] M. F. Newman, J. P. Mathew, H. P. Grocott et al., "Central nervous system injury associated with cardiac surgery," *The Lancet*, vol. 368, no. 9536, pp. 694–703, 2006.
- [35] G. M. McKhann, M. A. Grega, L. M. Borowicz Jr., W. A. Baumgartner, and O. A. Selnes, "Stroke and encephalopathy after cardiac surgery: an update," *Stroke*, vol. 37, no. 2, pp. 562–571, 2006.
- [36] H. P. Grocott, "Pharmacologic neuroprotection: the search continues," *Journal of Extra-Corporeal Technology*, vol. 39, no. 4, pp. 296–301, 2007.
- [37] A. Dumas, G. H. Dupuis, N. Searle, and R. Cartier, "Early versus late extubation after coronary artery bypass grafting: effects on cognitive function," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 13, no. 2, pp. 130–135, 1999.
- [38] N. P. Dowd, J. M. Karski, D. C. Cheng et al., "Fast-track cardiac anaesthesia in the elderly: effect of two different anaesthetic techniques on mental recovery," *British Journal of Anaesthesia*, vol. 86, no. 1, pp. 68–76, 2001.
- [39] T. Bottio, G. Bisleri, P. Piccoli, A. Negri, A. Manzato, and C. Muneretto, "Heart valve surgery in a very high-risk population: a preliminary experience in awake patients," *Journal of Heart Valve Disease*, vol. 16, no. 2, pp. 187–194, 2007.
- [40] E. Delphin, D. Jackson, Y. Gubenko et al., "Sevoflurane provides earlier tracheal extubation and assessment of cognitive recovery than isoflurane in patients undergoing off-pump coronary artery bypass surgery," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 21, no. 5, pp. 690–695, 2007.
- [41] M. Kanbak, F. Saricaoglu, S. B. Akinçi et al., "The effects of isoflurane, sevoflurane, and desflurane anesthesia on neurocognitive outcome after cardiac surgery: a pilot study," *The Heart Surgery Forum*, vol. 10, no. 1, pp. E36–E41, 2007.
- [42] J. A. Hudetz, Z. Iqbal, S. D. Gandhi et al., "Ketamine attenuates post-operative cognitive dysfunction after cardiac surgery," *Acta Anaesthesiologica Scandinavica*, vol. 53, no. 7, pp. 864–872, 2009.
- [43] J. Schoen, L. Husemann, C. Tiemeyer et al., "Cognitive function after sevoflurane- vs propofol-based anaesthesia for on-pump cardiac surgery: a randomized controlled trial," *British Journal of Anaesthesia*, vol. 106, no. 6, pp. 840–850, 2011.
- [44] Y. Kadoi, S. Saito, F. Kunitomo, F. Goto, and N. Fujita, "Comparative effects of propofol versus fentanyl on cerebral oxygenation state during normothermic cardiopulmonary bypass and post-operative cognitive dysfunction," *Annals of Thoracic Surgery*, vol. 75, no. 3, pp. 840–846, 2003.
- [45] B. S. Silbert, D. A. Scott, L. A. Evered et al., "A comparison of the effect of high- and low-dose fentanyl on the incidence of postoperative cognitive dysfunction after coronary artery bypass surgery in the elderly," *Anesthesiology*, vol. 104, no. 6, pp. 1137–1145, 2006.
- [46] Y. Kadoi and F. Goto, "Sevoflurane anesthesia did not affect postoperative cognitive dysfunction in patients undergoing coronary artery bypass graft surgery," *Journal of Anesthesia*, vol. 21, no. 3, pp. 330–335, 2007.
- [47] A. Lehmann, M. Schmidt, C. Zeitler, A.-H. Kiessling, F. Isagro, and J. Boldt, "Bispectral index and electroencephalographic entropy in patients undergoing aortocoronary bypass grafting," *European Journal of Anaesthesiology*, vol. 24, no. 9, pp. 751–760, 2007.
- [48] L. Evered, D. A. Scott, B. Silbert, and P. Maruff, "Postoperative cognitive dysfunction is independent of type of surgery and anesthetic," *Anesthesia and Analgesia*, vol. 112, no. 5, pp. 1179–1185, 2011.
- [49] V. M. Parra, M. Sadurní, M. Doñate et al., "Neuropsychological dysfunction after cardiac surgery: cerebral saturation and bispectral index: a longitudinal study," *Revista Medica de Chile*, vol. 139, no. 12, pp. 1553–1561, 2011.
- [50] C. F. Royse, D. T. Andrews, S. N. Newman et al., "The influence of propofol or desflurane on postoperative cognitive dysfunction in patients undergoing coronary artery bypass surgery," *Anaesthesia*, vol. 66, no. 6, pp. 455–464, 2011.
- [51] R. F. Gottesman, A. E. Hillis, M. A. Grega et al., "Early postoperative cognitive dysfunction and blood pressure during coronary artery bypass graft operation," *Archives of Neurology*, vol. 64, no. 8, pp. 1111–1114, 2007.
- [52] M. F. Newman, D. Kramer, N. D. Croughwell et al., "Differential age effects of mean arterial pressure and rewarming on cognitive dysfunction after cardiac surgery," *Anesthesia and Analgesia*, vol. 81, no. 2, pp. 236–242, 1995.
- [53] R. L. Patel, M. R. J. Turtle, D. J. Chambers, S. Newman, and G. E. Venn, "Hyperperfusion and cerebral dysfunction. Effect of differing acid-base management during cardiopulmonary bypass," *European Journal of Cardio-Thoracic Surgery*, vol. 7, no. 9, pp. 457–464, 1993.
- [54] R. L. Patel, M. R. Turtle, D. J. Chambers, D. N. James, S. Newman, and G. E. Venn, "Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuropsychologic outcome in patients undergoing coronary artery bypass grafting," *Journal of Thoracic and Cardiovascular Surgery*, vol. 111, no. 6, pp. 1267–1279, 1996.
- [55] A. V. Govier, J. G. Reves, R. D. McKay et al., "Factors and their influence on regional cerebral blood flow during nonpulsatile cardiopulmonary bypass," *Annals of Thoracic Surgery*, vol. 38, no. 6, pp. 592–600, 1984.
- [56] G. Wimmer-Greinecker, G. Matheis, M. Brieden et al., "Neuropsychological changes after cardiopulmonary bypass for coronary artery bypass grafting," *Thoracic and Cardiovascular Surgeon*, vol. 46, no. 4, pp. 207–212, 1998.
- [57] H. Jönsson, P. Johnsson, C. Ailing, M. Bäckström, C. Bergh, and S. Blomquist, "S100beta after coronary artery surgery: release pattern, source of contamination, and relation to neuropsychological outcome," *Annals of Thoracic Surgery*, vol. 68, no. 6, pp. 2202–2208, 1999.
- [58] S. Kilminster, T. Treasure, T. McMillan, and D. W. Holt, "Neuropsychological change and S-100 protein release in 130 unselected patients undergoing cardiac surgery," *Stroke*, vol. 30, no. 9, pp. 1869–1874, 1999.
- [59] L. S. Rasmussen, M. Christiansen, P. B. Hansen, and J. T. Møller, "Do blood levels of neuron-specific enolase and S-100 protein reflect cognitive dysfunction after coronary artery bypass?" *Acta Anaesthesiologica Scandinavica*, vol. 43, no. 5, pp. 495–500, 1999.
- [60] D. N. Derkach, H. Okamoto, and S. Takahashi, "Neuronal and astroglial injuries in patients undergoing coronary artery bypass

- grafting and aortic arch replacement during hypothermic cardiopulmonary bypass," *Anesthesia and Analgesia*, vol. 91, no. 5, pp. 1066–1072, 2000.
- [61] A. Diegeler, R. Hirsch, F. Schneider et al., "Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation," *Annals of Thoracic Surgery*, vol. 69, no. 4, pp. 1162–1166, 2000.
- [62] D. Georgiadis, A. Berger, E. Kowatschev et al., "Predictive value of S-100 β and neuron-specific enolase serum levels for adverse neurologic outcome after cardiac surgery," *Journal of Thoracic and Cardiovascular Surgery*, vol. 119, no. 1, pp. 138–147, 2000.
- [63] C. T. Lloyd, R. Ascione, M. J. Underwood, F. Gardner, A. Black, and G. D. Angelini, "Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 119, no. 1, pp. 148–154, 2000.
- [64] A. M. Basile, C. Fusi, A. A. Conti et al., "S-100 protein and neuron-specific enolase as markers of subclinical cerebral damage after cardiac surgery: preliminary observation of a 6-month follow-up study," *European Neurology*, vol. 45, no. 3, pp. 151–159, 2001.
- [65] L. S. Rasmussen, M. Christiansen, K. Eliassen, K. Sander-Jensen, and J. T. Møller, "Biochemical markers for brain damage after cardiac surgery—time profile and correlation with cognitive dysfunction," *Acta Anaesthesiologica Scandinavica*, vol. 46, no. 5, pp. 547–551, 2002.
- [66] B. Farsak, S. Gunaydin, C. Yorgancioglu, and Y. Zorlutuna, "Elevated levels of s-100 β correlate with neurocognitive outcome after cardiac surgery," *Journal of Cardiovascular Surgery*, vol. 44, no. 1, pp. 31–35, 2003.
- [67] J. P. Mathew, H. P. Grocott, B. Phillips-Bute et al., "Lower endotoxin immunity predicts increased cognitive dysfunction in elderly patients after cardiac surgery," *Stroke*, vol. 34, no. 2, pp. 508–513, 2003.
- [68] H. Jönsson, P. Johnsson, M. Bäckström, C. Alling, C. Dautovic-Bergh, and S. Blomquist, "Controversial significance of early S100B levels after cardiac surgery," *BMC Neurology*, vol. 4, article 24, 2004.
- [69] W. A. Kofke, P. Konitzer, Q. C. Meng, J. Guo, and A. Cheung, "The effect of apolipoprotein E genotype on neuron specific enolase and S-100 β levels after cardiac surgery," *Anesthesia & Analgesia*, vol. 99, no. 5, pp. 1323–1325, 2004.
- [70] S. A. Snyder-Ramos, T. Gruhlke, H. Bauer et al., "Cerebral and extracerebral release of protein S100B in cardiac surgical patients," *Anaesthesia*, vol. 59, no. 4, pp. 344–349, 2004.
- [71] J. Kálmán, A. Juhász, G. Bogáts et al., "Elevated levels of inflammatory biomarkers in the cerebrospinal fluid after coronary artery bypass surgery are predictors of cognitive decline," *Neurochemistry International*, vol. 48, no. 3, pp. 177–180, 2006.
- [72] B. Ramlawi, J. L. Rudolph, S. Mieno et al., "C-Reactive protein and inflammatory response associated to neurocognitive decline following cardiac surgery," *Surgery*, vol. 140, no. 2, pp. 221–226, 2006.
- [73] J. P. Mathew, H. P. Grocott, J. R. McCurdy II et al., "Preoperative statin therapy does not reduce cognitive dysfunction after cardiopulmonary bypass," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 19, no. 3, pp. 294–299, 2005.
- [74] K. Plaschke, S. Hauth, C. Jansen et al., "The influence of preoperative serum anticholinergic activity and other risk factors for the development of postoperative cognitive dysfunction after cardiac surgery," *Journal of Thoracic and Cardiovascular Surgery*, vol. 145, no. 3, pp. 805–811, 2013.
- [75] G. Grieco, M. d'Hollosy, A. T. Culliford, and S. Jonas, "Evaluating neuroprotective agents for clinical anti-ischemic benefit using neurological and neuropsychological changes after cardiac surgery under cardiopulmonary bypass. Methodological strategies and results of a double-blind, placebo-controlled trial of GM1 ganglioside," *Stroke*, vol. 27, no. 5, pp. 858–874, 1996.
- [76] J. E. Arrowsmith, M. J. G. Harrison, S. P. Newman, J. Stygall, N. Timberlake, and W. B. Pugsley, "Neuroprotection of the brain during cardiopulmonary bypass: a randomized trial of remacemide during coronary artery bypass in 171 patients," *Stroke*, vol. 29, no. 11, pp. 2357–2362, 1998.
- [77] L. G. Svensson, E. M. Nadolny, and W. A. Kimmel, "Multimodal protocol influence on stroke and neurocognitive deficit prevention after ascending/arch aortic operations," *Annals of Thoracic Surgery*, vol. 74, no. 6, pp. 2040–2046, 2002.
- [78] R. Uebelhack, K. Vohs, M. Zytowski, H.-J. Schewe, C. Koch, and W. Konertz, "Effect of piracetam on cognitive performance in patients undergoing bypass surgery," *Pharmacopsychiatry*, vol. 36, no. 3, pp. 89–93, 2003.
- [79] I. Szalma, Á. Kiss, L. Kardos et al., "Piracetam prevents cognitive decline in coronary artery bypass: a randomized trial versus placebo," *Annals of Thoracic Surgery*, vol. 82, no. 4, pp. 1430–1435, 2006.
- [80] G. Haljan, A. Maitland, A. Buchan et al., "The erythropoietin neuroprotective effect: assessment in CABG surgery (TENPEAKS): a randomized, double-blind, placebo controlled, proof-of-concept clinical trial," *Stroke*, vol. 40, no. 8, pp. 2769–2775, 2009.
- [81] Z. Zhang, P. Ma, Y. Xu et al., "Preventive effect of gastrodin on cognitive decline after cardiac surgery with cardiopulmonary bypass: a double-blind, randomized controlled study," *Journal of Huazhong University of Science and Technology: Medical Science*, vol. 31, no. 1, pp. 120–127, 2011.
- [82] R. S. Kong, J. Butterworth, W. Aveling et al., "Clinical trial of the neuroprotectant clomethiazole in coronary artery bypass graft surgery: a randomized controlled trial," *Anesthesiology*, vol. 97, no. 3, pp. 585–591, 2002.
- [83] D. P. Taggart, S. M. Browne, D. T. Wade, and P. W. Halligan, "Neuroprotection during cardiac surgery: a randomised trial of a platelet activating factor antagonist," *Heart*, vol. 89, no. 8, pp. 897–900, 2003.
- [84] J. P. Mathew, M. L. Fontes, I. C. Tudor et al., "A multicenter risk index for atrial fibrillation after cardiac surgery," *The Journal of the American Medical Association*, vol. 291, no. 14, pp. 1720–1729, 2004.
- [85] C. W. Hogue Jr., K. Freedland, T. Hershey et al., "Neurocognitive outcomes are not improved by 17 β -estradiol in postmenopausal women undergoing cardiac surgery," *Stroke*, vol. 38, no. 7, pp. 2048–2054, 2007.
- [86] S. Holinski, B. Claus, N. Alaraj et al., "Cerebroprotective effect of piracetam in patients undergoing open heart surgery," *Annals of Thoracic and Cardiovascular Surgery*, vol. 17, no. 2, pp. 137–142, 2011.
- [87] M. Grimm, M. Czerny, H. Baumer et al., "Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting—a prospective randomized trial," *European Journal of Cardio-Thoracic Surgery*, vol. 18, no. 3, pp. 270–275, 2000.

- [88] M. Shaaban-Ali, M. Harmer, R. S. Vaughan et al., "Changes in serum S100 β protein and mini-mental state examination after cold (28°C) and warm (34°C) cardiopulmonary bypass using different blood gas strategies (alpha-stat and pH-stat)," *Acta Anaesthesiologica Scandinavica*, vol. 46, no. 1, pp. 10–16, 2002.
- [89] H. J. Nathan, J. Munson, G. Wells, C. Mundi, F. Balaa, and J. E. Wynands, "The management of temperature during cardiopulmonary bypass: effect on neuropsychological outcome," *Journal of Cardiac Surgery*, vol. 10, no. 4, pp. 481–487, 1995.
- [90] H. P. Grocott, G. B. Mackensen, A. M. Grigore et al., "Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery," *Stroke*, vol. 33, no. 2, pp. 537–541, 2002.
- [91] Y. Kadoi, S. Saito, K.-I. Takahashi, N. Fujita, and F. Goto, "Jugular venous oxygen saturation during mild hypothermic versus normothermic cardiopulmonary bypass in elderly patients," *Surgery Today*, vol. 34, no. 5, pp. 399–404, 2004.
- [92] M. Boodhwani, F. D. Rubens, D. Wozny et al., "Predictors of early neurocognitive deficits in low-risk patients undergoing on-pump coronary artery bypass surgery," *Circulation*, vol. 114, no. 1, pp. 1461–1466, 2006.
- [93] K. Hiraoka, S. Kawatsu, E. Mori, and Y. Saiki, "Total aortic arch replacement using hypothermic circulatory arrest with antegrade selective cerebral perfusion: are there cerebral deficits other than frank stroke?" *General Thoracic and Cardiovascular Surgery*, vol. 60, no. 6, pp. 345–349, 2012.
- [94] R. F. McLean, B. I. Wong, C. D. Naylor et al., "Cardiopulmonary bypass, temperature, and central nervous system dysfunction," *Circulation*, vol. 90, no. 5, pp. II250–II255, 1994.
- [95] I. Regragui, I. Birdi, M. B. Izzat et al., "The effects of cardiopulmonary bypass temperature on neuropsychologic outcome after coronary artery operations: a prospective randomized trial," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 112, no. 4, pp. 1036–1045, 1996.
- [96] E. J. Heyer, D. C. Adams, E. Delphin et al., "Cerebral dysfunction after coronary artery bypass grafting done with mild or moderate hypothermia," *Journal of Thoracic and Cardiovascular Surgery*, vol. 114, no. 2, pp. 270–277, 1997.
- [97] A. C. Kneebone, M. J. Andrew, R. A. Baker, and J. L. Knight, "Neuropsychologic changes after coronary artery bypass grafting: use of reliable change indices," *Annals of Thoracic Surgery*, vol. 65, no. 5, pp. 1320–1325, 1998.
- [98] D. L. Reich, S. Uysal, M. Sliwinski et al., "Neuropsychologic outcome after deep hypothermic circulatory arrest in adults," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 117, no. 1, pp. 156–163, 1999.
- [99] L. Kaukinen, H. Porkkala, S. Kaukinen et al., "Release of brain-specific creatine kinase and neuron-specific enolase into cerebrospinal fluid after hypothermic and normothermic cardiopulmonary bypass in coronary artery surgery," *Acta Anaesthesiologica Scandinavica*, vol. 44, no. 4, pp. 361–368, 2000.
- [100] R. Górna, W. Kustrzycki, A. Kiejna, and J. Rymaszewska, "Assessment of short-term neuropsychologic changes after normothermic versus hypothermic coronary artery bypass grafting," *Psychiatria Polska*, vol. 35, no. 5, pp. 781–795, 2001.
- [101] A. M. Grigore, J. Mathew, H. P. Grocott et al., "Prospective randomized trial of normothermic versus hypothermic cardiopulmonary bypass on cognitive function after coronary artery bypass graft surgery," *Anesthesiology*, vol. 95, no. 5, pp. 1110–1119, 2001.
- [102] H. Kaukuntla, A. Walker, D. Harrington, T. Jones, and R. S. Bonser, "Differential brain and body temperature during cardiopulmonary bypass—a randomised clinical study," *European Journal of Cardio-thoracic Surgery*, vol. 26, no. 3, pp. 571–579, 2004.
- [103] D. L. Reich, L. M. Horn, S. Hossain, and S. Uysal, "Using jugular bulb oxyhemoglobin saturation to guide onset of deep hypothermic circulatory arrest does not affect post-operative neuropsychological function," *European Journal of Cardio-Thoracic Surgery*, vol. 25, no. 3, pp. 401–408, 2004.
- [104] T. Kuniyama, D. Tscholl, F. Langer, G. Heinz, F. Sata, and H.-J. Schäfers, "Cognitive brain function after hypothermic circulatory arrest assessed by cognitive P300 evoked potentials," *European Journal of Cardio-Thoracic Surgery*, vol. 32, no. 3, pp. 507–513, 2007.
- [105] C. T. Mora, M. B. Henson, W. S. Weintraub et al., "The effect of temperature management during cardiopulmonary bypass on neurologic and neuropsychologic outcomes in patients undergoing coronary revascularization," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 112, no. 2, pp. 514–522, 1996.
- [106] H. J. Nathan, G. A. Wells, J. L. Munson, and D. Wozny, "Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: a randomized trial," *Circulation*, vol. 104, no. 1, pp. i85–i91, 2001.
- [107] A. M. Grigore, H. P. Grocott, J. P. Mathew et al., "The rewarming rate and increased peak temperature alter neurocognitive outcome after cardiac surgery," *Anesthesia & Analgesia*, vol. 94, no. 1, pp. 4–10, 2002.
- [108] F. Kawahara, Y. Kadoi, S. Saito, F. Goto, and N. Fujita, "Slow rewarming improves jugular venous oxygen saturation during rewarming," *Acta Anaesthesiologica Scandinavica*, vol. 47, no. 4, pp. 419–424, 2003.
- [109] H. J. Nathan, R. Rodriguez, D. Wozny et al., "Neuroprotective effect of mild hypothermia in patients undergoing coronary artery surgery with cardiopulmonary bypass: five-year follow-up of a randomized trial," *The Journal of Thoracic and Cardiovascular Surgery*, vol. 133, no. 5, pp. 1206–1211, 2007.
- [110] B. Sahu, S. Chauhan, U. Kiran et al., "Neurocognitive function in patients undergoing coronary artery bypass graft surgery with cardiopulmonary bypass: the effect of two different rewarming strategies," *Journal of Cardiothoracic and Vascular Anesthesia*, vol. 23, no. 1, pp. 14–21, 2009.