

Cerebral Autoregulation in Cardiopulmonary Bypass Surgery: A Systematic Review

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ABSTRACT

Background: Cardiopulmonary bypass surgery is associated with a high incidence of neurological complications, including stroke, delirium and cognitive impairment. The development of strategies to reduce the incidence of such neurologic events has been hampered by the lack of a clear understanding of their pathophysiology. Cerebral autoregulation (CA), which describes the brain's ability to maintain a stable cerebral blood flow over a wide range of cerebral perfusion pressures despite changes in blood pressure, is known to be impaired in various neurological disorders. Therefore, we aimed to systematically review studies reporting indices of CA in cardiopulmonary bypass surgery. **Methods:** Databases MEDLINE, Web of Science, Cochrane Database of Systematic Reviews and EMBASE were searched for relevant articles. Titles, abstracts and full texts of articles were scrutinized according to pre-defined selection criteria. Two independent reviewers undertook the methodological quality screening and data extraction of the included studies. **Results:** Twenty of 2,566 identified studies were relevant. Studies showed marked heterogeneity and weaknesses in key methodological criteria (e.g. population size and discussion of limitations). All but three of the 20 studies described impairments of CA with cardiac surgery. Eleven studies investigated clinical outcomes, and nine of these found a significant relationship between these and impaired CA. **Conclusions:** There is general agreement that cardiac surgery is associated with changes in CA, and that clinical outcomes appear to be significantly related to impaired CA. Further studies are now needed to determine prognostic significance, and to inform future therapeutic strategies.

Key words: Cardiac surgery, cerebrovascular circulation, cerebral blood flow regulation, heart surgery.

INTRODUCTION

Despite continual advancements in surgical and anesthetic techniques, and improvements in cardiopulmonary bypass (CPB) technology, neurological complications remain one of the major hazards of cardiac surgery. The causes of these complications are still not fully established or understood [1]. However, as the complexity of surgical procedures increases and the population ages, neurological complications including adverse cognitive outcomes are of increasing concern. Indeed, postoperative cognitive impairment is found in as many as 69% of patients undergoing cardiac surgery at the time of hospital discharge [2]. Furthermore, delirium affects up to 70% of high risk patients, and strokes occurs in up to 6% of patients after cardiac surgery [3,4].

The development of strategies to reduce the incidence of such postoperative neurologic complications has been hampered by a lack of clear understanding of their pathophysiology. It was believed that the main mechanism of cerebral injury after cardiac surgery was the use of CPB [5]. However, recent studies have not shown a significant risk reduction with the use of off-pump surgery [6–9]. Another traditionally invoked mechanism of brain injury was that of macro- and micro-embolization, but few studies have shown a robust correlation between the number of emboli and cognitive outcomes [11,12]. Furthermore, a recently published study did not find significant associations between neurological complications and the presence, size, or number of new lesions on MRI [12].

Several neurological disorders with a significant incidence and considerable impact on quality of life, including stroke, head trauma, carotid artery disease and subarachnoid hemorrhage, involve disturbances of cerebral blood flow (CBF) and its regulatory mechanisms [13–15]. However, the effect of cardiac surgery on cerebral autoregulation (CA) is not known. CA is the brain's ability to maintain a stable CBF over a wide range of different cerebral perfusion pressures (CPP) despite changes in blood pressure (BP), typically in the range 60–150 mmHg [16]. Autoregulation is accomplished via a complex interplay of myogenic, chemical, metabolic and neurogenic mechanisms, and is affected by various factors including arterial blood pressure (BP), intracranial pressure (ICP), arterial PaCO₂, mental activation and posture. If CA is impaired, changes in BP can lead to cerebral ischemia or to edema or microvascular damage due to excessive CBF [17]. Methodologically, it is

important to distinguish between static and dynamic CA. The former, and more classical approach, uses steady-state measurements of CBF and BP, usually manipulated through the use of pharmacological agents [14–16,18]. The latter assesses both the efficacy and latency of transient changes in CBF (or CBF velocity) following rapid changes in BP [13,15,17–21].

Cerebral hemodynamics can be assessed using transcranial Doppler (TCD). The temporal resolution of TCD has allowed the analysis of transient CBF velocity (CBFV) responses to induced and spontaneous changes in BP [17]. Near-infrared spectroscopy (NIRS), another non-invasive method that measures regional cerebral oxygen saturation (rScO₂), can also be used, as well as other modalities of CBF measurement [22,23–25]. Nevertheless, the individual results have been difficult to interpret, and the overall effect of CPB on CA is not clear. Therefore, the aim of this systematic review was to report in full the literature that has investigated the effects of CPB on CA, in order to improve understanding of the pathophysiology of neurological complications.

MATERIALS AND METHODS

Search strategy

A literature search in the bibliographic databases MEDLINE, Web of Science, Cochrane Database of Systematic Reviews and EMBASE was undertaken by the first author and an independent researcher (VH) using the following search terms:

Cardiac surgery OR heart surgery OR heart procedures OR thoracic surgery AND cerebral autoregulation OR cerebral haemodynamics OR cerebral hemodynamics OR cerebrovascular circulation OR cerebral blood flow regulation.

Different MeSH terms or subcategories available on the search databases were truncated to increase the sensitivity of the search. The references and citation indices of selected articles were hand-searched for additional relevant articles. Peer-reviewed studies detailing the quantification of CA before, during, or after CPB surgery were included. Eligibility was assessed by reading abstracts and, if necessary, whole articles.

Inclusion and Exclusion Criteria

All identified references published between June 1967 and August 2016 and featuring adult human subjects were eligible for review. References were excluded if they were case reports, abstracts, dissertations, pediatric or animal studies, studies involving operations other than cardiac surgery with CPB, non-English language articles, studies that did not specify the type of cardiac surgery, or studies that did not include a measurement of CBF. Case reports and studies of cardiac procedures such as angioplasty, angiography, valvuloplasty, and Transcatheter Aortic Valve Implantation (TAVI) were also excluded.

Data Extraction

The following data were extracted: (1) population; (2) number of patients and controls; (3) time of measurements; (4) CA challenges (input); (5) method of data analysis; (6) autoregulation evaluation method (steady-state vs. dynamic autoregulation); (7) clinical outcome; (8) main conclusions of the study; and (9) status of CA.

Two authors (JRC, VH) evaluated the selected studies in terms of quality using a checklist adapted from authors, editors, and reviews of meta-analyses of observational studies using 15 relevant items [26,27].

Statistical analysis

Because of significant differences in study methodologies, heterogeneity of the CA indices reported, and a uniform lack of control data, meta-analysis could not be performed. Instead, a descriptive systematic review was completed.

RESULTS

Study selection

A total of 2,566 citations were identified. After dismissing duplicates, non-relevant topics, and studies where CBF was not quantified, 36 38 abstracts remained (Fig. 1). Eight of these studies were subsequently excluded because CA was described using CBF measurement in isolation, without the

quantification of BP. Five further studies were excluded as they similarly reported cerebral oxygen saturation without reporting BP. A further three were excluded as they reported CO₂ reactivity, and not CA. One was excluded because it reported effects of drugs on CA, confounding the effect of CPB. One final study was excluded because it was a trial registration without results. Hence, 20 publications were eligible for review [22–25,28–43].

Study details are summarized in Table 1. The median score on the quality checklist was 11 (range 7–13), reflecting incomplete reporting of key methodological criteria in the majority of studies.

Study characteristics and measurement techniques

Study size varied from eight to 491 patients. Only two studies analyzed CA at five periods: baseline, before CPB, during CPB, after CPB, and following surgery (Table 1) [37,40]. CA was evaluated with various imaging modalities: four studies evaluated CA using TCD [23,24,32,33], five used NIRS [25,34,39,41,42], two used ultrasound-tagged NIRS (UT-NIRS) [29,40], six used TCD and NIRS, [22,28,30,36,37,43], two used TCD and UT-NIRS [31,38], and ¹³³Xe clearance was used in just one study [35]. Twelve different indices, detailed in Table 2, were used to report CA in these studies. These are summarized in Fig. 2. Information about clinical course and outcome after the surgery in relation to CA was provided in eleven studies [23–25,28,29,36,39–43].

Cerebral autoregulation before cardiac surgery

Seven studies assessed CA in patients before surgery [24,29,31,32,34,36,37], and six of these also described CA during surgery [29,31,32,34,36,37]. All but two of the seven studies analyzed CA through static methods [29,31,34,36,37]. Dynamic CA was reported with autoregulation index (ARI) [32] and), rate of dynamic autoregulation recovery (RoR) [23] indices. Two studies used UT- NIRS [29, 31] and two studies used NIRS [34. 37]. None of these studies concluded that CA was impaired before surgery.

Cerebral autoregulation during cardiac surgery

All but two of the 20 studies reported values of CA during CPB [23,24]. Nine studies [22,25,28,30,33,35,38,39,41] exclusively reported intra-operative CA; no pre- or post-operative measurements were made. Of the 18 studies reporting intra-operative CA, all but two [35,40] described impairments of CA with surgery. However, it should be noted that these impairments were only statistically significant in seven studies [29,31,32,33,34,36,43]. Of the remainder, two [22,38] were validation studies of the utility of NIRS during CPB; their statistical models were therefore used to compare intra-operative TCD measurements to NIRS values, rather than to assess CA changes per se. Nevertheless, they described trends consistent with impaired CA during surgery. Four further studies [30,37,41,42] also described trends to impaired CA, or values outside pre-determined CA thresholds, but did not provide statistical confirmation. Three studies [25,28,39] reported the percentage of patients who had impaired CA during CPB, with values of 19%, 20% and 11.7%, respectively. One study, which determined CA using both cerebral oxygen saturation (Cox) and mean velocity index (Mx) (Table 2), found CA to be impaired according to COx, but not Mx, thresholds [22]. One study reported that hemodilution and hypercapnia in CPB negatively affected CA [32], and two studies reported that the largest change in CA was observed during the rewarming phase of CPB [36,43].

Cerebral autoregulation after cardiac surgery

Nine papers analyzed CA after CPB and surgery [23,24,29,31,36,37,40,42,43]. However, it should be noted that the majority of post-operative recordings were made immediately after cessation of CPB; only two studies made an assessment of CA in the ICU after surgery [29,40]; one at three hours [29] and one at day 1 [40]. Six studies showed that CA recovered after CPB, and three reported impaired CA post-operatively [29,37,40]. Of these, two [29,40] simply described values outside the pre-determined limits of autoregulation but did not provide statistical confirmation, and one [37] reported that 30% of patients had abnormal CA as determined by a COx ≥ 0.3 .

Clinical outcomes and cerebral autoregulation

Eleven studies reported clinical outcomes in the context of CA and CPB [23–25,28,29,36,39–43], although one of these simply stated that no patients suffered from gross neurological deficit after the operation [24]. This study notably reported static (sCA) and dynamic (RoR) CA in patients undergoing CPB, and found no significant changes in either. In studies where clinical outcomes were reported in more detail, they were: major mortality and morbidity (defined as operative death, stroke, renal failure, mechanical lung ventilation >48h or low cardiac output syndrome, acute kidney injury, stroke, post-operative cognitive decline, and delirium). Duration and magnitude of mean arterial pressure (MAP) less than the lower limit of autoregulation was found to be an independent risk factor for major mortality and morbidity [25]. Similarly, patients who had excursions of BP outside CA limits were also more likely to develop acute kidney injury (AKI) [39]. More specifically, the lower limit of CA was found to be increased in patients who developed AKI [29]. The relationship of impaired CA and stroke is a little less clear; one study reported no statistically significant differences in the autoregulation parameters Mx and COx between patients who suffered stroke [28] and those without neurological injury, whilst two [36,44] found a significantly increased risk of peri-operative stroke if CA was impaired, as determined by Mx. The single study reporting post-operative cognitive decline found that poorer performance on the Stroop Color Word Test was associated with a higher gain [23]. Both studies investigating CA and post-operative delirium found significant relationships [40,41]; the risk of delirium was four-fold higher in those patients whose MAP exceeded the upper (but not the lower) limit of autoregulation [41], and excursions of BP above the determined optimal MAP were associated with both the incidence and severity of delirium on postoperative day 2 [40].

DISCUSSION

There is general agreement that cardiac surgery is associated with changes in CA, with 17 of the 20 studies reporting that CA is impaired with CPB. None of these studies concluded that CA was impaired before surgery and the majority of these showed that CA recovered after CPB. All but two of these studies assessed CA through a static method. Another key finding is that nine out of the eleven studies investigating clinical outcomes, including stroke, acute kidney injury, delirium and mortality, found a significant relationship between these and impaired CA.

Impairment of CA renders the brain less tolerant to both low and high MAP, with increased risks of significant brain oligemia and hyperemia respectively. Multiple studies have shown an association of CA impairment with neurological disorders. Although there is significant variation in the imaging modalities, study protocols, timing of CA measurements, and indices used to evaluate CA during CPB surgery, this review adds to the existing literature on cerebral hemodynamic abnormalities in cardiac surgery and indicates that impaired CA may play an important role in the development of neurological complications after cardiac surgery with CPB.

Postoperative brain injury significantly contributes to increased morbidity and mortality, and has negative consequences on quality of life and costs [5,45,46]. Three of the most commonly encountered neurological deficits are postoperative stroke, delirium and cognitive decline [46]. In our review, only three studies investigated the link between impaired CA during CPB and postoperative stroke [28, 36, 44] with conflicting results. However, stroke continues to be one of the most debilitating and devastating complications of cardiac surgery. Although there is some evidence to suggest that the incidence may be decreasing slightly, the overall rate of stroke has remained remarkably constant at between 1% and 3% [47].

Our results indicate that impaired CA following cardiac surgery is associated with a higher incidence of post-operative delirium. Delirium is an acute disorder of awareness and attention that has a fluctuating course common after cardiac surgery, and is associated with additional new cognitive decline, post-operative stroke, increased morbidity, length of hospitalization, hospital readmission and mortality [4,46–48]. Cerebral hyperperfusion due to impaired autoregulation has been suggested as the mechanism for delirium occurring in nonsurgical patients with acute hypertensive emergencies [49]. Prevention in high-risk patients, and early detection and treatment of those affected is therefore important to minimize poor outcomes.

Owing partly to the assumption that adverse neurologic events were specifically related to the use of extracorporeal CPB, techniques have been developed for performing cardiac surgery without the use of CPB ('off-pump' surgery). However, recent large, prospective, randomized studies comparing the rates of adverse neurologic outcomes after conventional on-pump surgery with those after off-

pump surgery have not shown a significant risk reduction associated with the use of off-pump surgery [6–9].

Although the pathogenesis of adverse neurologic events after cardiac surgery is probably multifactorial, there is growing evidence that patient-related risk factors are particularly relevant [50]. Of particular concern, given the potential for increased complications, are older patients with pre-existing cerebral vascular disease. In this review, six studies assessed CA in patients before surgery, but did not show impaired CA. This is surprising, as it is known that patients undergoing cardiac surgery have a higher prevalence of conditions such as heart failure, diabetes and carotid artery disease, all of which are associated with impaired CA [19,51]. Understanding the significance of impaired pre-operative CA therefore has considerable potential to improve models for the prediction of brain damage after cardiac surgery, and warrants further investigation.

Limitations of the study

There are several limitations to this review. Firstly, and most importantly, the interpretation of the effect of cardiac surgery on CA is hampered by various methodological issues. The studies included used different imaging modalities and indices to quantify CA. This is reflective of the numerous methods of quantification of CA in use at the current time, each with their own inherent assumptions, caveats and specific experimental models. Importantly, no particular method is currently considered to be the ‘gold-standard’, but the available indices of CA have notably been shown to yield largely divergent results for the same data [20] and should thus be scrutinized carefully. Furthermore, definitions and assessments of post-operative complications varied between studies, making direct comparisons difficult. Secondly, data were missing, or insufficient, in several of the studies making complete reporting difficult. Thirdly, the cut-offs used to define impaired CA varied between studies, and all had been arbitrarily determined. The variation in scores on the quality checklists also indicates incomplete reporting of key methodological criteria in the majority of studies. Nonetheless, despite these limitations, in combination these studies strongly suggest that CA is impaired by CPB surgery.

Accordingly, whilst the pathogenesis of neurological sequelae after CPB surgery is likely to be multifactorial, it appears that impairment of CA may well be a key factor.

Conclusions and Further Work

Unfortunately, neurological sequelae remains an important complication of cardiac surgery, despite significant advances in operative techniques. Given the implication that CPB surgery is associated with impaired CA, further work is now needed to elucidate the exact underlying mechanisms of impaired CA in CPB surgery, and to understand causality between impaired CA and poor neurological outcomes. Such work has the potential to inform strategies to reduce postoperative neurological complications. Future study goals are therefore: (1) the determination of CA before, during and after surgery; (2) the development of multivariate models to better understand the exact mechanisms of CA impairment; (3) evaluation of the course of CA over time; (4) evaluation of CA in patients undergoing off-pump surgery; and (5) quantification of the impact of CA impairment on outcomes with clinically relevant cut-off points.

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CONFLICT OF INTEREST: none declared.

FIGURES LEGENDS

Figure 1. Flow diagram of the study selection process

Figure 2. Overview of the linear models and analytical methods used in autoregulation studies in this systematic review.

Table 1. Characteristics of identified publications examining cerebral autoregulation on cardiac surgery with bypass

STUDY	N	AGE	TYPE OF SURGERY	INDEX	BASE LINE	DURING	AFTER CPB	AFTER SURGERY	MAIN RESULTS AND CONCLUSIONS
-TDC									
Ševerdija, 2015 [33]	37	61 ± 6	CABG	ARI		30 mmHg PCO ₂			During CPB CA parameters were significantly higher (p < 0.01) during hypocapnia compared with both normocapnia and hypercapnia.
						6 ± 1			
						Coherence			
						0.90 ± 0.10			
						Gain			
						3.4 ± 2.0			
						Phase			
						0.6 ± 0.3			
						40 mmHg PCO ₂			
						ARI			
						5 ± 1			
						Coherence			
Ševerdija, 2015 [32]	40	60.1 [55.8-68.6]	CABG	ARI	7.5[7.0-8.0]	Ht >28			ARI lower during CPB compared to pre-operative values suggesting impaired intra-operative CA. ARI adversely affected by haemodilution and hypercapnia.
						6.1[5.5-6.5] PaCO ₂ 4kpa			
						5.6[4.6-6.2] PaCO ₂ 5.3kPa			
						3.3[2.5-4.2] PaCO ₂ 6.6 Kpa			
						Ht < 28			
						5.5[4.1-6.2] PaCO ₂ /4kpa			
						4.4[3.9-5.1] PaCO ₂ 5.3 kPa			
						2.6[1.6-3.7] PaCO ₂ 6.6 Kpa			
Preisman, 2005 [24]	12	64 (49–78)	CABG	sCA RoR	sCA 76.4 ± 22.6 RoR 0.22 ± 0.04		15 min		CVR reduces after CPB, but static and dynamic CA are preserved.
							sCA 80.2 ±12.4		
							RoR 0.20 ± 0.09		
							30 min		
							sCA 73.6 ± 14.3		
							RoR 0.21 ± 0.10)		
Christiansen, 2015 [23]	8	63 ± 10.1	CABG	Gain Phase Coherence			45 min		No difference between patients and 10 healthy controls.
							sCA 74.4 ± 14.6		
							RoR 0.23 ± 0.14		
Christiansen, 2015 [23]	8	63 ± 10.1	CABG	Gain Phase Coherence			1.2 (0.94-1.49)		No difference between patients and 10 healthy controls.
							0.33 (0.15-0.56)		
							0.86 (0.77-0.91)		

Table 1 Continued.

STUDY	N	AGE	TYPE OF SURGERY	INDEX	BASE LINE	DURING	AFTER CPB	AFTER SURGERY	MAIN RESULTS AND CONCLUSIONS
- TCD + UT-NIRS									
Murkin, 2015 [31]	20	63.5 ± 11.3		CFI CFIx Mx	8.6 ± 2.5	6.6 ± 2.3	9.0 ± 3.4		45% of patients demonstrated impaired CA prior to CPB, 30% of patients demonstrated impairment of CA during CPB, and 20% demonstrated impaired CA after CPB. Only 5% of patients had worsening of CA after CPB. Impaired CA defined as Mx or CFIx ≤ 0.35
Hori, 2015 [38]	64	65 ± 8.8	CABG 32 CABG + Valve 8 Valve 2 Others* 4	Mx CFVx		Mx left 0.31 ± 0.17 Mx right 0.32 ± 0.17 CFVx left 0.33 ± 0.19 CFVx right 0.35 ± 0.19			Significant correlation and agreement between index. Average Mx values <0.4 suggesting preserved CA intra-operatively.
- TCD + NIRS									
Ono, 2012 [37]	10	62 ± 10	CABG	Mx Cox	0.10 ± 0.13	0.42 ± 0.14 7 (70%) patients had abnormal AR	0.31 ± 0.14 4 (40%) patients had abnormal AR	3 patients (30%) had abnormal AR on day 1 post-operatively (COx)	7 (70%) patients had abnormal CA during CPB. Abnormal CA defined as Mx ≥ 0.4/ COx ≥ 0.3
Easley, 2013 [36]	109	65 ± 11	CABG 73 CABG + Valve 8 Valve 23 Others* 5	Mx					Increasing Mx values (suggestive of worsening CA) over the course of the CPB (p < 0.0001). Greatest change observed during rewarming.
Ono, 2013 [22]	70	61 ± 12	CABG 33 CABG + Valve 19 Valve 9 Others* 6	Mx Cox		0.27 ± 0.16 0.34 ± 0.21			Mx did not impair during CPB, but COx impaired (thresholds for impairment ≥ 0.4 and ≥ 0.3 respectively).
Brady, 2010 [30]	60	64 ± 13	CABG 36 CABG + Valve 19 Valve 9	Mx		0.38 (95% CI: 0.34-0.43)			CA was disturbed during CPB. Mx cutoff for disturbed CA 0.3-0.5.
Ono, 2012 [28]	234	Intact AR 66 (52–88) Impaired AR 66 (46–89)	CABG 113 CABG + Valve 26 Valve 34 Others* 8	Mx Cox		Intact AR 0.27 ± 0.12 Impaired AR 0.52 ± 0.08 Intact AR 0.24 ± 0.16 Impaired AR 0.37 ± 0.16			47 (20%) patients demonstrated impaired CA during CPB. Impaired CA defined as Mx ≥ 0.4. Peri-operative stroke was more common in patients with impaired CA
Joshi, 2010 [43]	127	65 ± 11	CABG 76 CABG + Valve 18 Valve 30 Others* 3	Mx	left 0.17 ± 0.21 right 0.17 ± 0.20	left 0.40 ± 0.19 right 0.39 ± 0.19	left 0.27 ± 0.20 right 0.28 ± 0.21		Mx increased during the rewarming phase of CPB) compared with baseline (P = 0.0001). After CPB but before wound closure, Mx was higher than at baseline. All 7 strokes that occurred perioperatively were in patients with impaired CBF autoregulation during CPB rewarming.

STUDY	N	AGE	TYPE OF SURGERY	INDEX	BASE LINE	DURING	AFTER CPB	AFTER SURGERY	MAIN RESULTS AND CONCLUSIONS
- UT-NIRS									
Hori, 2016 [29]	110	65 ± 8.8	CABG 58 CABG + Valve 16 Valve 34 Others* 2	CFx	0.33±0.17		0.12±0.10		There was a significant decrease in average CFx in ICU compared with that measured during CPB (P < 0.0001), indicating better preserved average CA after surgery with return of pulsatile flow.
Hori, 2016 [40]	110	65 ± 8.8	CABG 50 CABG + Valve 11 Valve 32 Others* 6	CFx	Delirium 0.27 ± 0.16 No delirium 0.29 ± 0.16	Delirium 0.34 ± 0.16 No delirium 0.34 ± 0.19	Delirium 0.25 ± 0.16 No delirium 0.29 ± 0.16	Delirium 0.09 ± 0.12 No Delirium 0.14 ± 0.08	No significant differences in CFx both before and after CPB. However, impaired CA is associated with delirium on postoperative day 2.
- NIRS									
Hori, 2015 [42]	121	71 ± 8.1	CABG 66 CABG + Valve 25 Valve 22 Others* 8	COx OptMAP		Average MAP 75±6.5 mmHg OptMAP 78±12.8 mmHg	Average MAP 74±7.3 mmHg (p=0.008)		54% of patients experienced hypotension in ICU based on COx. Patients who had average MAP in the ICU below their OptMAP, determined from COx monitoring during CPB, had significantly higher plasma GFAP levels on post-operative day 1 compared with patients whose MAP remained above the optimal level in ICU.
Hori, 2014 [41]	491	66.2 ± 11.3	CABG 277 CABG + Valve 70 Valve 106 Others* 38	COx ULA		3.448 <LLA 0.422>ULA			LLA defined as that decrement of MAP at which Cox increased from <0.3 to > 0.3. ULA defined as that incremental increase in MAP at which COx increased from <0.3 to >0.3. Frequency of delirium four-fold higher in patients whose MAP exceeded ULA, but no different with LLA.
Hori, 2016 [34]	197	71 ± 8.0	CABG 105 CABG + Valve 38 Valve 45 Others* 9	COx	0.18 [0.07–0.27]	There was a significant increase in COx			COx value significantly increased from baseline during CPB (p<0.001).
Ono, 2014 [25]	450	No MMOM 66 ± 11 MMOM 68 ± 11	CABG 262 CABG + Valve 62 Valve 99 Others* 14	COx		No MMOM 0.27 ± 0.18 MMOM 0.26 ± 0.17			A dysregulated pattern (COx ≥0.3 at all MAPs) was observed in 83 patients (19%).Duration and magnitude of MAP less than LLA independent risk factor for MMOM.
Ono, 2013 [39]	410	66 ± 11	CABG 217 CABG + Valve 49 Valve 82	COx		48 patients COx ≥0.3 at all MAPs			In 48 (11.7%) patients, COx was ≥0.3 at all MAPs, and in 14 patients, no clear autoregulation threshold could be determined. Duration and degree MAP outside the autoregulatory thresholds increased in patients with AKI.

Table 1 Continued.

STUDY	N	AGE	TYPE OF SURGERY	INDEX	BASE LINE	DURING	AFTER CPB	AFTER SURGERY	MAIN RESULTS AND CONCLUSIONS
- 133 Xe injection									
Ti, 2001 [35]	91	61 ± 69 59 ± 61	CABG	Relationship of CBF to MAP and CMRO2					CBF increased in response to increased CRMO ₂ , but did not change in response to changes in MAP signifying preserved CA.

TDC, transcranial Doppler; CABG, coronary artery bypass grafting; ARI, autoregulation index; PCO2, partial pressure of carbon dioxide, CBP, cardiopulmonary bypass; CA, cerebral autoregulation, Ht, hematocrit; sCA static cerebral autoregulation; RoR, rate of dynamic autoregulation recovery; CVR, cerebrovascular resistance; COx, cerebral oxygen saturation index; AR, autoregulation; MAP, mean arterial pressure; OptMAP, optimal MAP; ICU, intensive care unit; ULA, upper limit of A1:L32 LLA, lower limit of autoregulation; MMOM, major morbidity and operative mortality; AKI, acute kidney injury; CFx, correlation flow index; CFVx, cerebral flow velocity index; CFix, cerebral flow index correlation index; Mx, mean velocity index; CBF, cerebral blood flow; CMRO2, cerebral metabolic rate for oxygen. Others* (aortic root, ascending aneurysm

Table 2. Indices of static and dynamic CA used by studies of CA in cardiac surgery with CPB

INDEX	DEFINITION	STATIC/ DYNAMIC	REFERENCES (20 selected studies)
COx	correlation coefficient between MAP and rScO ₂	S	[22, 25, 28, 30, 34, 37, 39, 41, 42]
ARI	Autoregulation index [16]	D	[32, 33]
Coherence	Fraction of CBFV power, linearly explained by MAP at each frequency	D	[23, 33]
Phase	TFA phase lag between CBFV and MAP at each frequency [52]	D	[23, 33]
Gain	TFA amplitude between CBFV and BP at each frequency [52]	D	[23, 33]
CFx CFIx CFVx	Correlation coefficient between changes in MAP and microcirculatory blood flow by UT- NIRS	S*	[29, 31, 39, 40]
Mx	Moving Pearson's correlation coefficient between CBFV and MAP.	S*	[22, 30, 28, 36, 37, 40, 43]
Metabolism-flow autoregulation	Change in CBF at two different values of CMRO ₂ from hypothermia to normothermia	S	[35]
Pressure-flow autoregulation	change in CBF at two different MAP	S	[35]
sCA	change of CVRi related to change of CPP during the Trendelenburg manoeuvre	S	[24]
RoR	ratio of slope of CBFV recovery normalised by BP after thigh cuff release	D	[24]

*Does not inform latency of the response

COx, cerebral oxygen saturation index; MAP, mean arterial pressure, rScO₂, regional cerebral oxygen saturation; ARI, autoregulation index; CBFV, cerebral blood flow velocity; TFA transfer function analysis; CFx, correlation flow index, CFVx, cerebral flow velocity index; CFIx, cerebral flow index correlation index; Mx mean velocity index; CBF, cerebral blood flow; CMRO₂, cerebral metabolic rate for oxygen; sCA static cerebral autoregulation; CVRi, cerebrovascular resistance index; CPP, cerebral perfusion pressure; RoR, rate of dynamic autoregulation recovery.

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