Interactive CardioVascular and Thoracic Surgery (2017) 1–10
doi:10.1093/icvts/ivx357



Cite this article as: Caldas JR, Haunton VJ, Panerai RB, Hajjar LA, Robinson TG. Cerebral autoregulation in cardiopulmonary bypass surgery: a systematic review. Interact CardioVasc Thorac Surg 2017; doi:10.1093/icvts/ivx357.



# Cerebral autoregulation in cardiopulmonary bypass surgery: a systematic review

Juliana R. Caldas[a,b,*], Victoria J. Haunton[c], Ronney B. Panerai[c,d], Ludhmila A. Hajjar[a,e] and Thompson G. Robinson[c,d]

[a] Department of Anesthesia, Heart Institute, University of São Paulo, São Paulo, Brazil
[b] Hospital Sao Rafael, Salvador, Bahia, Brazil
[c] Department of Cardiovascular Sciences, University of Leicester, Leicester, UK
[d] NIHR Leicester Biomedical Research Centre, University of Leicester, Leicester, UK
[e] Department of Cardiopneumology, Heart Institute, University of São Paulo, Brazil

* Corresponding author. Surgical Intensive Care, Heart Institute, University of São Paulo, Av. Dr. Enéas de Carvalho Aguiar 44, 05403-000 São Paulo, Brazil. Tel: +551-126-615367; e-mail: caldas.juliana@gmail.com (J.R. Caldas).

Received 11 May 2017; received in revised form 30 August 2017; accepted 3 October 2017

## Abstract

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 neurological events has been hampered by the lack of a clear understanding of their pathophysiology. Cerebral autoregulation (CA), which describes the ability of the brain 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. Databases such as 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 predefined selection criteria. Two independent reviewers undertook the methodological quality screening and data extraction of the included studies. Twenty of 2566 identified studies were relevant. Studies showed marked heterogeneity and weaknesses in key methodological criteria (e.g. population size and discussion of limitations). All but 3 of the 20 studies described impairments of CA with cardiac surgery. Eleven studies investigated clinical outcomes, and 9 of these found a significant relationship between these and impaired CA. There is a 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.

**Keywords:** Cardiac surgery • Cerebrovascular circulation • Cerebral blood flow regulation • Heart surgery

## INTRODUCTION

Despite continual advancements in surgical and anaesthetic 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 occur in up to 6% of patients after cardiac surgery [3, 4].

The development of strategies to reduce the incidence of such postoperative neurological 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 microembolization, but few studies have shown a robust correlation between the number of emboli and cognitive outcomes [10–12]. Furthermore, a recently published study did not find significant associations between neurological complications and the presence, size or number of new lesions on magnetic resonance imaging [12].

Several neurological disorders with a significant incidence and considerable impact on quality of life, including stroke, head trauma, carotid artery disease and subarachnoid haemorrhage, 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 ability of the brain to maintain a stable CBF over a wide range of different cerebral perfusion pressures 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 BP, intracranial pressure, arterial partial pressure of carbon dioxide, mental activation and posture. If CA is impaired, changes in BP can lead to cerebral ischaemia or to oedema 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 the latency of transient changes in CBF [or CBF velocity (CBFV)] following rapid changes in BP [13, 15, 17–21].

Cerebral haemodynamics can be assessed using transcranial Doppler (TCD). The temporal resolution of TCD has allowed the analysis of transient CBFV responses to induced and spontaneous changes in BP [17]. Near-infrared spectroscopy (NIRS), another non-invasive method that measures regional cerebral oxygen saturation, 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 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 (V.H.) using the following search terms:

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

Different medical subject headings (MeSH) terms or subcategories available on the search databases were truncated to increase the sensitivity of the search. The references and citation indices of the 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, paediatric 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 were also excluded.

### Data extraction

The following data were extracted: (i) population; (ii) number of patients and controls; (iii) time of measurements; (iv) CA challenges (input); (v) method of data analysis; (vi) autoregulation evaluation method (steady-state versus dynamic autoregulation); (vi) clinical outcome; (viii) main conclusions of the study and (ix) status of CA.

Two authors (J.R.C. and V.H.) 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 2566 citations were identified. After dismissing duplicates, non-relevant topics and studies where CBF was not quantified, 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 3 were excluded as they reported carbon dioxide 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 8 to 491 patients. Only 2 studies analysed CA at 5 periods: baseline, before CPB, during CPB, after CPB and following surgery (Table 1) [37, 40]. CA was evaluated with various imaging modalities: 4 studies evaluated CA using TCD [23, 24, 32, 33], 5 used NIRS [25, 34, 39, 41, 42], 2 used ultrasound-tagged NIRS [29, 40], 6 used TCD and NIRS, [22, 28, 30, 36, 37, 43], 2 used TCD and ultrasound-tagged NIRS [31, 38] and $^{133}$Xe clearance was used in just 1 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 11 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 6 of these also described CA during surgery [29, 31, 32, 34, 36, 37]. All but 2 of the 7 studies analysed CA through static methods [29, 31, 34, 36, 37]. Dynamic CA was reported with autoregulation index [32] and rate of dynamic

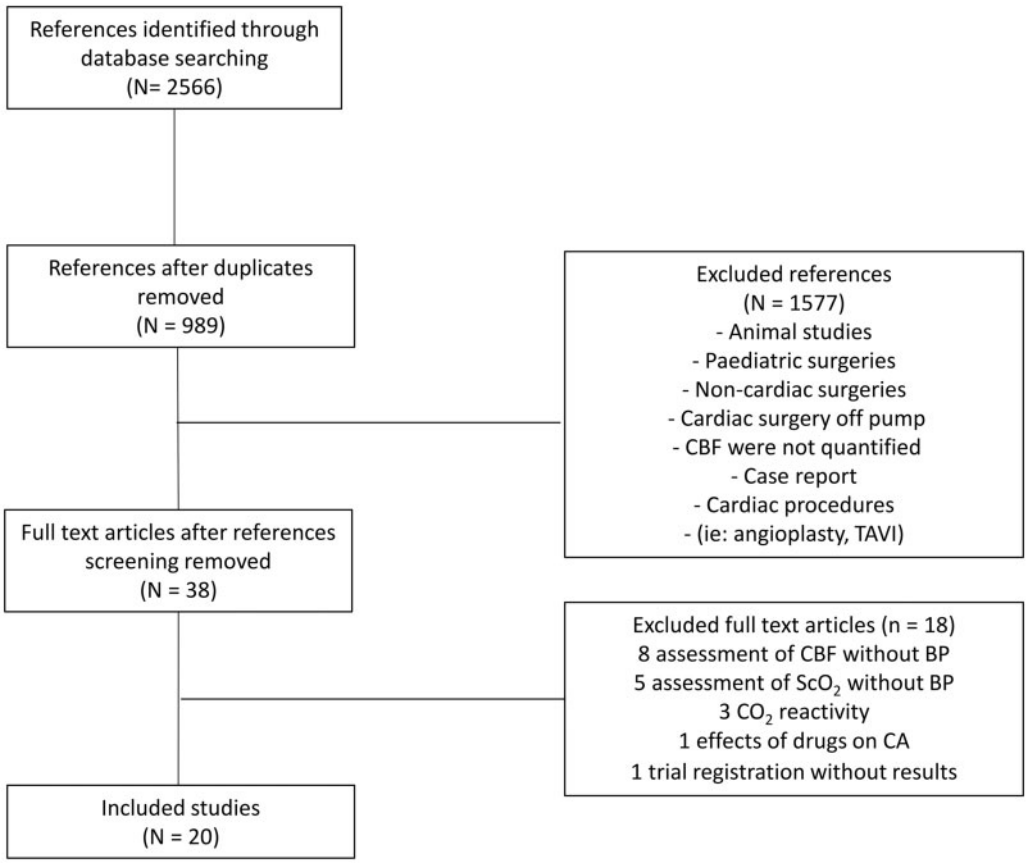


**Figure 1:** Flow diagram of the study selection process. CA: cerebral autoregulation; CBF: cerebral blood flow; $CO_2$: carbon dioxide; $ScO_2$: cerebral oxygen saturation; TAVI: transcatheter aortic valve implantation.

autoregulation recovery [23] indices. Two studies used ultrasound-tagged NIRS [29, 31] and 2 studies used NIRS [34, 37]. None of these studies concluded that CA was impaired before surgery.

## Cerebral autoregulation during cardiac surgery

All but 2 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 intraoperative CA; no pre- or postoperative measurements were made. Of the 18 studies reporting intraoperative CA, all but 2 [35, 40] described impairments of CA with surgery. However, it should be noted that these impairments were only statistically significant in 7 studies [29, 31–34, 36, 43]. Of the remainder, 2 [22, 38] were validation studies of the utility of NIRS during CPB; their statistical models were therefore used to compare intraoperative TCD measurements with 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 predetermined 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 oximetry index (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 haemodilution and hypercapnia in CPB negatively affected CA [32], and 2 studies reported that the largest change in CA was observed during the rewarming phase of CPB [36, 43].

## Cerebral autoregulation after cardiac surgery

Nine articles analysed CA after CPB and surgery [23, 24, 29, 31, 36, 37, 40, 42, 43]. However, it should be noted that the majority of postoperative recordings were made immediately after cessation of CPB; only 2 studies made an assessment of CA in the intensive care unit after surgery [29, 40]; 1 at 3 h [29] and 1 at Day 1 [40]. Six studies showed that CA recovered after CPB, and 3 reported impaired CA postoperatively [29, 37, 40]. Of these, 2 [29, 40] simply described values outside the predetermined limits of autoregulation but did not provide statistical confirmation, and 1 [37] reported that 30% of patients had abnormal CA as determined by a Cox $\geq$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 and dynamic (rate of dynamic autoregulation recovery) CA in patients undergoing CPB and found no significant changes in both. Studies where clinical outcomes were reported in more detail included major mortality and morbidity (defined as operative death, stroke, renal failure, mechanical lung ventilation >48 h or

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

| Study | *n* | Age | Type of surgery | Index | Baseline | During | After CPB | After surgery | Main results and conclusions |
|---|---|---|---|---|---|---|---|---|---|
| TCD | | | | | | | | | |
| Ševerdija *et al.* [33] | 37 | 61 ± 6 | CABG | ARI<br>Coherence<br>Gain<br>Phase<br><br>ARI<br>Coherence<br>Gain<br>Phase<br><br>ARI<br>Coherence<br>Gain<br>Phase | | 30 mmHg $PCO_2$<br>6 ± 1<br>0.90 ± 0.10<br>3.4 ± 2.0<br>0.6 ± 0.3<br>40 mmHg $PCO_2$<br>5 ± 1<br>0.91 ± 0.09<br>2.2 ± 0.9<br>0.3 ± 0.2<br>50 mmHg $PCO_2$<br>3 ± 2<br>0.95 ± 0.06<br>1.4 ± 0.4<br>0.1 ± 0.1 | | | During CPB, CA parameters were significantly higher ($P < 0.01$) during hypocapnia compared with both normocapnia and hypercapnia |
| Ševerdija *et al.* [32] | 40 | 60.1 (55.8–68.6) | CABG | ARI | 7.5 (7.0–8.0) | Ht > 28<br>6.1 (5.5–6.5) $PaCO_2$ 4 kPa<br>5.6 (4.6–6.2) $PaCO_2$ 5.3 kPa<br>3.3 (2.5–4.2) $PaCO_2$ 6.6 kPa<br>Ht < 28<br>5.5 (4.1–6.2) $PaCO_2$/4 kPa<br>4.4 (3.9–5.1) $PaCO_2$ 5.3 kPa<br>2.6 (1.6–3.7) $PaCO_2$ 6.6 kPa | | | ARI lower during CPB compared with preoperative values, suggesting impaired intraoperative CA. ARI adversely affected by haemodilution and hypercapnia |
| Preisman *et al.* [24] | 12 | 64 (49–78) | CABG | sCA<br>RoR | sCA 76.4 ± 22.6<br>RoR 0.22 ± 0.04 | | 15 min<br>sCA 80.2 ± 12.4<br>RoR 0.20 ± 0.09<br>30 min<br>sCA 73.6 ± 14.3<br>RoR 0.21 ± 0.10)<br>45 min<br>sCA 74.4 ± 14.6<br>RoR 0.23 ± 0.14 | | CVR reduces after CPB, but static and dynamic CA are preserved |
| Christiansen *et al.* [23] | 8 | 63 ± 10.1 | CABG | Gain<br>Phase<br>Coherence | | | 1.2 (0.94–1.49)<br>0.33 (0.15–0.56)<br>0.86 (0.77–0.91) | | No difference between patients and 10 healthy controls |
| TCD + UT-NIRS | | | | | | | | | |
| Murkin *et al.* [31] | 20 | 63.5 ± 11.3 | | CFI<br>CFIx<br>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.<br>Only 5% of patients had worsening of CA after CPB. Impaired CA defined as Mx or CFIx $\leq$ 0.35 |

*Continued*

**Table 1:** Continued

| Study | *n* | Age | Type of surgery | Index | Baseline | During | After CPB | After surgery | Main results and conclusions |
|---|---|---|---|---|---|---|---|---|---|
| Hori *et al.* [38] | 64 | 65 ± 8.8 | CABG 32<br>CABG+<br>Valve 8<br>Valve 2<br>Others* 4 | Mx<br><br><br><br>CFVx | | Mx left<br>0.31 ± 0.17<br>Mx right<br>0.32 ± 0.17<br>CFVx left<br>0.33 ± 0.19<br>CFVx right<br>0.35 ± 0.19 | | | Significant correlation and agreement between index. Average Mx values <0.4, suggesting preserved CA intraoperatively |
| TCD + NIRS | | | | | | | | | |
| Ono *et al.* [37] | 10 | 62 ± 10 | CABG | Mx<br>Cox | 0.10 ± 0.13 | 0.42 ± 0.14<br>7 (70%) patients had abnormal AR | 0.31 ± 0.14<br>4 (40%) patients had abnormal AR | 3 patients (30%) had abnormal AR on Day 1 postoperatively (COx) | 7 (70%) patients had abnormal CA during CPB<br>Abnormal CA defined as Mx ≥ 0.4/COx ≥ 0.3 |
| Easley *et al.* [36] | 109 | 65 ± 11 | CABG 73<br>CABG+<br>Valve 8<br>Valve 23<br>Others* 5 | Mx | | | | | Increasing Mx values (suggestive of worsening CA) over the cours of the CPB ($P < 0.0001$). Greatest change observed during rewarming |
| Ono *et al.* [22] | 70 | 61 ± 12 | CABG 33<br>CABG+<br>Valve 19<br>Valve 9<br>Others* 6 | Mx<br><br>Cox | | 0.27 ± 0.16<br><br>0.34 ± 0.21 | | | Mx did not impair during CPB, but COx impaired (thresholds for impairment ≥0.4 and ≥0.3, respectively |
| Brady *et al.* [30] | 60 | 64 ± 13 | CABG 36<br>CABG+<br>Valve 19<br>Valve 9 | Mx | | 0.38<br>(95% CI 0.34–0.43) | | | CA was disturbed during CPB. Mx cut-off for disturbed CA 0.3–0.5 |
| Ono *et al.* [28] | 234 | Intact AR<br>66 (52–88)<br>Impaired AR<br>66 (46–89) | CABG 113<br>CABG+<br>Valve 26<br>Valve 34<br>Others* 8 | Mx<br><br><br><br>Cox | | Intact AR<br>0.27 ± 0.12<br>Impaired AR<br>0.52 ± 0.08<br>Intact AR<br>0.24 ± 0.16<br>Impaired AR<br>0.37 ± 0.16 | | | 47 (20%) patients demonstrated impaired CA during CPB. Impaired CA defined as Mx ≥0.4. Perioperative stroke was more common in patients with impaired CA |
| Joshi *et al.* [43] | 127 | 65 ± 11 | CABG 76<br>CABG+<br>Valve 18<br>Valve 30<br>Others* 3 | Mx | left<br>0.17 ± 0.21<br>right<br>0.17 ± 0.20 | left<br>0.40 ± 0.19<br>right<br>0.39 ± 0.19 | left<br>0.27 ± 0.20<br>right<br>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 |
| UT-NIRS | | | | | | | | | |
| Hori *et al.* [29] | 110 | 65 ± 8.8 | CABG 58<br>CABG+<br>Valve 16<br>Valve 34<br>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 |

*Continued*

**Table 1:** Continued

| Study | *n* | Age | Type of surgery | Index | Baseline | During | After CPB | After surgery | Main results and conclusions |
|---|---|---|---|---|---|---|---|---|---|
| Hori *et al.* [40] | 110 | 65 ± 8.8 | CABG 50<br>CABG+<br>Valve 11<br>Valve 32<br>Others* 6 | CFx | Delirium<br>0.27 ± 0.16<br>No delirium<br>0.29 ± 0.16 | Delirium<br>0.34 ± 0.16<br>No delirium<br>0.34 ± 0.19 | Delirium<br>0.25 ± 0.16<br>No delirium<br>0.29 ± 0.16 | Delirium<br>0.09 ± 0.12<br>No Delirium<br>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 *et al.* [42] | 121 | 71 ± 8.1 | CABG 66<br>CABG+<br>Valve 25<br>Valve 22<br>Others* 8 | Cox<br><br>OptMAP | | Average MAP<br><br>75 ± 6.5 mmHg<br>OptMAP<br>78 ± 12.8 mmHg | | Average MAP<br>74 ± 7.3 mmHg<br>($P$ = 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 postoperative Day 1 compared with patients whose MAP remained above the optimal level in ICU |
| Hori *et al.* [41] | 491 | 66.2 ± 11.3 | CABG 277<br>CABG+<br>Valve 70<br>Valve 106<br>Others* 38 | Cox<br>ULA | | 3.448 < LLA<br>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 4-fold higher in patients whose MAP exceeded ULA, but no different with LLA |
| Hori *et al.* [34] | 197 | 71 ± 8.0 | CABG 105<br>CABG+<br>Valve 38<br>Valve 45<br>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 *et al.* [25] | 450 | No MMOM<br>66 ± 11<br>MMOM<br>68 ± 11 | CABG 262<br>CABG+<br>Valve 62<br>Valve 99<br>Others* 14 | COx | | No MMOM<br>0.27 ± 0.18<br>MMOM<br>0.26 ± 0.17 | | | A dysregulated pattern (COx ≥0.3 at all MAPs) was observed in 83 (19%) patients. Duration and magnitude of MAP less than LLA was an independent risk factor for MMOM |
| Ono *et al.* [39] | 410 | 66 ± 11 | CABG 217<br>CABG+<br>Valve 49<br>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 |
| $^{133}$Xe injection | | | | | | | | | |
| Ti *et al.* [35] | 91 | 61 ± 69<br>59 ± 61 | CABG | Relationship of CBF to MAP and $CMRO_2$ | | | | | CBF increased in response to increased $CRMO_2$ but did not change in response to changes in MAP signifying preserved CA |

Others* indicates aortic root, ascending aneurysm.

AKI: acute kidney injury; AR: autoregulation; ARI: autoregulation index; CA: cerebral autoregulation; CABG: coronary artery bypass grafting; CBF: cerebral blood flow; CPB: cardiopulmonary bypass; CFx: correlation flow index; CFIx: cerebral flow index correlation index; CFVx: cerebral flow velocity index; CI: confidence interval; $CMRO_2$: cerebral metabolic rate for oxygen; COx: cerebral oximetry index; CVR: cerebrovascular resistance; GFAP: glial fibrillary acidic protein plasma levels; Ht: haematocrit; ICU: intensive care unit; LLA: lower limit of autoregulation; MAP: mean arterial pressure; MMOM: major morbidity and operative mortality; Mx: mean velocity index; OptMAP: optimal mean arterial pressure; $PaCO_2$: arterial partial pressure of carbon dioxide ; $PCO_2$: partial pressure of carbon dioxide; RoR: rate of dynamic autoregulation recovery; sCA: static cerebral autoregulation; TCD: transcranial Doppler; ULA: upper limit of A1:L32; UT-NIRS: ultrasound-tagged near-infrared spectroscopy.

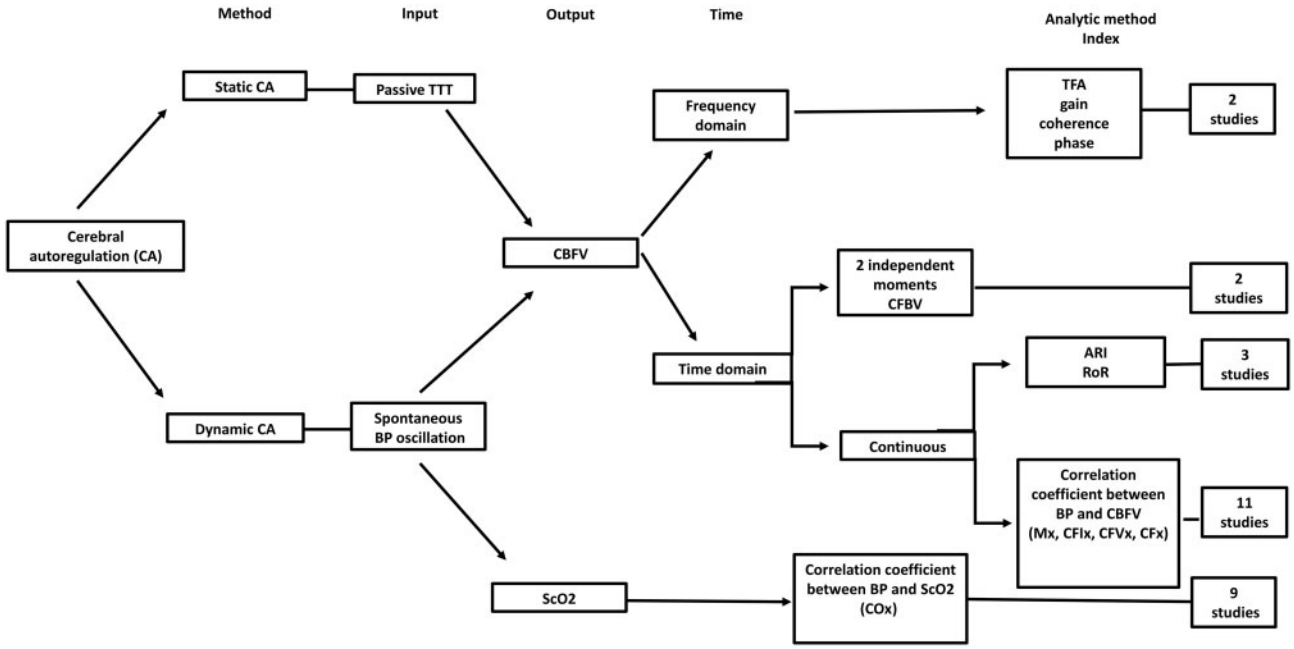


**Figure 2:** Overview of the linear models and analytical methods used in autoregulation studies in this systematic review. ARI: autoregulation index; BP: blood pressure; CA: cerebral autoregulation; CBFV: cerebral blood flow velocity; CFx: correlation flow index; CFIx: cerebral flow index correlation index; CFVx: cerebral flow velocity index; COx: cerebral oximetry index; Mx: mean velocity index; $ScO_2$: cerebral oxygen saturation; TFA: transfer function analysis; RoR: rate of dynamic autoregulation recovery; TTT: tilt test.

**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 rScO2 | 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 [44] | D | [23, 33] |
| Gain | TFA amplitude between CBFV and BP at each frequency [44] | D | [23, 33] |
| CFx<br>CFIx<br>CFVx | Correlation coefficient between changes in MAP and microcirculatory blood flow by UT-NIRS | S[a] | [29, 31, 39, 40] |
| Mx | Moving Pearson's correlation coefficient between CBFV and MAP | S[a] | [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] |

[a]Does not inform latency of the response.

ARI: autoregulation index; BP: blood pressure; CA: cerebral autoregulation; CBF: cerebral blood flow; CBFV: cerebral blood flow velocity; CFx: correlation flow index; CFIx: cerebral flow index correlation index; CFVx: cerebral flow velocity index; $CMRO_2$: cerebral metabolic rate for oxygen; COx: cerebral oximetry index; CPP: cerebral perfusion pressure; CVRi: cerebrovascular resistance index; MAP: mean arterial pressure; Mx: mean velocity index; RoR: rate of dynamic autoregulation recovery; $rScO_2$: regional cerebral oxygen saturation; sCA: static cerebral autoregulation; TFA: transfer function analysis; UT-NIRS: ultrasound-tagged-near-infrared spectroscopy.

low cardiac output syndrome, acute kidney injury, stroke, postoperative 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 [39]. More specifically, the lower limit of CA was found to be increased in patients who developed acute kidney injury [29]. The relationship of impaired CA and stroke is a little less clear; 1 study reported no statistically significant differences in the autoregulation parameters Mx and COx between patients who suffered stroke [28] and those without neurological injury, whereas 2 [36, 45] studies found a significantly increased risk of perioperative stroke if CA was impaired, as determined by Mx. The single study reporting postoperative cognitive decline found that poorer performance on the Stroop

Colour Word Test was associated with a higher gain [23]. Both studies investigating CA and postoperative delirium found significant relationships [40, 41]; the risk of delirium was 4-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 the 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 2 of these studies assessed CA through a static method. Another key finding is that 9 of the 11 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 oligaemia and hyperaemia, 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, and this review adds to the existing literature on cerebral haemodynamic 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, 46, 47]. Three of the most commonly encountered neurological deficits are postoperative stroke, delirium and cognitive decline [47]. In our review, only 3 studies investigated the link between impaired CA during CPB and postoperative stroke [28, 36, 45] 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% [48].

Our results indicate that impaired CA following cardiac surgery is associated with a higher incidence of postoperative 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, postoperative stroke, increased morbidity, length of hospitalization, hospital readmission and mortality [4, 47–49]. Cerebral hyperperfusion due to impaired autoregulation has been suggested as the mechanism for delirium occurring in non-surgical patients with acute hypertensive emergencies [50]. 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 neurological 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 neurological 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 neurological events after cardiac surgery is probably multifactorial, there is growing evidence that patient-related risk factors are particularly relevant [51]. Of particular concern, given the potential for increased complications, are older patients with pre-existing cerebral vascular disease. In this review, 6 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, 52]. Understanding the significance of impaired preoperative CA therefore has considerable potential to improve models for the prediction of brain damage after cardiac surgery and warrants further investigation.

### Limitations

There are several limitations to this review. First, and most important, 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 postoperative complications varied between studies, making direct comparisons difficult. Second, data were missing, or insufficient, in several of the studies making complete reporting difficult. Third, 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, although 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 remain 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 (i) the determination of CA before, during and after surgery; (ii) the development of multivariate models to better understand the exact mechanisms of CA impairment; (iii) evaluation of the course of CA over time; (iv) evaluation of CA in patients undergoing off-pump surgery and (v) quantification of the impact of CA impairment on outcomes with clinically relevant cut-off points.

**Conflict of interest:** none declared.

## REFERENCES


[1] Hindman BJ, Todd MM. Improving neurologic outcome after cardiac surgery. Anesthesiology 1999;90:1243–7.

[2] van Dijk D, Spoor M, Hijman R, Nathoe HM, Borst C, Jansen EW. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. JAMA 2007;297:701–8.

[3] Salazar JD, Wityk RJ, Grega MA, Borowicz LM, Doty JR, Petrofski JA *et al*. Stroke after cardiac surgery: short- and long-term outcomes. Ann Thorac Surg 2001;72:2.

[4] Brown CH. Delirium in the cardiac surgical ICU. Curr Opin Anaesthesiol 2014;27:117–22.

[5] Scolletta S, Taccone FS, Donadello K. Brain injury after cardiac surgery. Minerva Anestesiol 2015;81:662–77.

[6] Nathoe HM, van Dijk D, Jansen EW, Suyker WJ, Diephuis JC, Boven WJ. V *et al*. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. N Engl J Med 2003;348:394–402.

[7] Moller CH, Perko MJ, Lund JT, Andersen LW, Kelbaek H, Madsen JK *et al*. No major differences in 30-day outcomes in high-risk patients randomized to off-pump versus on-pump coronary bypass surgery: the best bypass surgery trial. Circulation 2010;121:498–504.

[8] Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. Lancet 2002;359:1194–9.

[9] Hueb W, Lopes NH, Pereira AC, Hueb AC, Soares PR, Favarato D *et al*. Five-year follow-up of a randomized comparison between off-pump and on-pump stable multivessel coronary artery bypass grafting. The MASS III Trial. Circulation 2010;122:48.

[10] Moody DM, Brown WR, Challa VR, Stump DA, Reboussin DM, Legault C. Brain microemboli associated with cardiopulmonary bypass: a histologic and magnetic resonance imaging study. Ann Thorac Surg 1995;59: 1304–7.

[11] Rodriguez RA, Rubens FD, Wozny D, Nathan HJ. Cerebral emboli detected by transcranial Doppler during cardiopulmonary bypass are not correlated with postoperative cognitive deficits. Stroke 2010;41: 2229–35.

[12] Patel N, Horsfield MA, Banahan C, Janus J, Masters K, Morlese J *et al*. Impact of perioperative infarcts after cardiac surgery. Stroke 2015;46: 680–6.

[13] Salinet AS, Panerai RB, Robinson TG. The longitudinal evolution of cerebral blood flow regulation after acute ischaemic stroke. Cerebrovasc Dis Extra 2014;4:186–97.

[14] Beek AH. V, Claassen JA, Rikkert MG, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. J Cereb Blood Flow Metab 2008;28:1071–85.

[15] Panerai RB. Assessment of cerebral pressure autoregulation in humans—a review of measurement methods. Physiol Meas 1998;19:305–38.

[16] Paulson OB, Strandgaard S, Edvinsson L. Cerebral autoregulation. Cerebrovasc Brain Metab Rev 1990;2:161–92.

[17] Panerai RB. Transcranial Doppler for evaluation of cerebral autoregulation. Clin Auton Res 2009;19:197–211.

[18] Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. Stroke 1995;26:1014–9.

[19] Panerai RB, White RP, Markus HS, Evans DH. Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. Stroke 1998;29:2341–6.

[20] Tzeng YC, Ainslie PN, Cooke WH, Peebles KC, Willie CK, MacRae BA *et al*. Assessment of cerebral autoregulation: the quandary of quantification. Am J Physiol Circ Physiol 2012;303:658.

[21] Aaslid R, Lindegaard KF, Sorteberg W, Nornes H. Cerebral autoregulation dynamics in humans. Stroke 1989;20:45–52.

[22] Ono M, Zheng Y, Joshi B, Sigl JC, Hogue CW. Validation of a stand-alone near-infrared spectroscopy system for monitoring cerebral autoregulation during cardiac surgery. Anesth Analg 2013;116:198–204.

[23] Christiansen CB, Berg RM, Plovsing R, Ronit A, Holstein-Rathlou NH, Yndgaard S *et al*. Dynamic cerebral autoregulation after cardiopulmonary bypass. Thorac Cardiovasc Surg 2015;64:569–74.

[24] Preisman S, Marks R, Nahtomi-Shick O, Sidi A. Preservation of static and dynamic cerebral autoregulation after mild hypothermic cardiopulmonary bypass. Br J Anaesth 2005;95:207–11.

[25] Ono M, Brady K, Easley RB, Brown C, Kraut M, Gottesman RF. Duration and magnitude of blood pressure below cerebral autoregulation threshold during cardiopulmonary bypass is associated with major morbidity and operative mortality. J Thorac Cardiovasc Surg 2014;147:483–9.

[26] Aries MJH, Elting JW, De J, Kremer BPH, Vroomen PCAJ. Cerebral autoregulation in stroke: a review of transcranial doppler studies. Stroke 2010; 41:2697–704.

[27] Salinet ASM, Haunton VJ, Panerai RB, Robinson TG. A systematic review of cerebral hemodynamic responses to neural activation following stroke. J Neurol 2013;260:2715–21.

[28] Ono M, Joshi B, Brady K, Easley RB, Zheng Y, Brown C *et al*. Risks for impaired cerebral autoregulation during cardiopulmonary bypass and postoperative stroke. Br J Anaesth 2012;109:391–8.

[29] Hori D, Hogue C, Adachi H, Max L, Price J, Sciortino C *et al*. Perioperative optimal blood pressure as determined by ultrasound tagged near infrared spectroscopy and its association with postoperative acute kidney injury in cardiac surgery patients. Interact CardioVasc Thorac Surg 2016;22:445–51.

[30] Brady K, Joshi B, Zweifel C, Smielewski P, Czosnyka M, Easley RB *et al*. Real-time continuous monitoring of cerebral blood flow autoregulation using near-infrared spectroscopy in patients undergoing cardiopulmonary bypass. Stroke 2010;41:1951–6.

[31] Murkin JM, Kamar M, Silman Z, Balberg M, Adams SJ. Intraoperative cerebral autoregulation assessment using ultrasound-tagged near-infrared-based cerebral blood flow in comparison to transcranial Doppler cerebral flow velocity: a pilot study. J Cardiothorac Vasc Anesth 2015;29:1187–93.

[32] Ševerdija EE, Vranken NPA, Simons AP, Gommer ED, Heijmans JH, Maessen JG *et al*. Hemodilution combined with hypercapnia impairs cerebral autoregulation during normothermic cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2015;29:1194–9.

[33] Ševerdija EE, Gommer ED, Weerwind PW, Reulen JPH, Mess WH, Maessen JG. Assessment of dynamic cerebral autoregulation and cerebral carbon dioxide reactivity during normothermic cardiopulmonary bypass. Med Biol Eng Comput 2015;53:195–203.

[34] Hori D, Ono M, Adachi H, Hogue CW. Effect of carotid revascularization on cerebral autoregulation in combined cardiac surgery. Eur J Cardiothorac Surg 2016;49:281–7.

[35] Ti LK, Mathew JP, Mackensen GB, Grocott HP, White WD, Reves JG *et al*. Effect of apolipoprotein E genotype on cerebral autoregulation during cardiopulmonary bypass. Stroke 2001;32:1514–9.

[36] Easley RB, Kibler KK, Brady KM, Joshi B, Ono M, Brown C *et al*. Continuous cerebrovascular reactivity monitoring and autoregulation monitoring identify similar lower limits of autoregulation in patients undergoing cardiopulmonary bypass. Neurol Res 2013;35:344–54.

[37] Ono M, Joshi B, Brady K, Easley RB, Kibler K, Conte J *et al*. Cerebral blood flow autoregulation is preserved after continuous-flow left ventricular assist device implantation. J Cardiothorac Vasc Anesth 2012;26:1022–8.

[38] Hori D, Hogue CW Jr, Shah A, Brown C, Neufeld KJ, Conte JV *et al*. Cerebral autoregulation monitoring with ultrasound-tagged near-infrared spectroscopy in cardiac surgery patients. Anesth Anal 2015;121: 1187–93.

[39] Ono M, Arnaoutakis GJ, Fine DM, Brady K, Easley RB, Zheng Y *et al*. Blood Pressure excursions below the cerebral autoregulation threshold during cardiac surgery are associated with acute kidney injury. Crit Care Med 2013;41:464–71.

[40] Hori D, Max L, Laflam A, Brown C, Neufeld KJ, Adachi H *et al*. Blood pressure deviations from optimal mean arterial pressure during cardiac surgery measured with a novel monitor of cerebral blood flow and risk for perioperative delirium: a pilot Study. J Cardiothorac Vasc Anesth 2016;30:606–12.

[41] Hori D, Brown C, Ono M, Rappold T, Sieber F, Gottschalk A *et al*. Arterial pressure above the upper cerebral autoregulation limit during cardiopulmonary bypass is associated with postoperative delirium. Br J Anaesth 2014;113:1009–17.

[42] Hori D, Ono M, Rappold TE, Conte JV, Shah AS, Cameron DE *et al*. Hypotension after cardiac operations based on autoregulation monitoring leads to brain cellular injury. Ann Thorac Surg 2015;100:487–93.

[43] Joshi B, Brady K, Lee J, Easley B, Panigrahi R, Smielewski P *et al*. Impaired autoregulation of cerebral blood flow during rewarming from hypothermic cardiopulmonary bypass and its potential association with stroke. Anesth Analg 2010;110:321–8.

[44] Claassen JA, Meel-van den Abeelen AS, Simpson DM, Panerai RB; (CARNet) international Cerebral Autoregulation Research Network. Transfer function analysis of dynamic cerebral autoregulation: a white paper from the International Cerebral Autoregulation Research Network. J Cereb Blood Flow Metab 2016;36:665–80.

[45] Joshi S, Wang M, Mayevsky A. Ultraviolet spectroscopy fails to reveal attenuation of brain tissue NADH increase by intravenous or intraarterial

propofol during transient cerebral hypoperfusion. J Neurosurg Anesthesiol 2009;21:374–5.
[46] Newman MF, Mathew JP, Grocott HP, Mackensen GB, Monk T, Welsh-Bohmer KA *et al*. Central nervous system injury associated with cardiac surgery. Lancet 2006;368:694–703.
[47] Cropsey C, Kennedy J, Han J, Pandharipande P. Cognitive dysfunction, delirium, and stroke in cardiac surgery patients. Semin Cardiothorac Vasc Anesth 2015;19:309–17.
[48] Filsoufi F, Rahmanian PB, Castillo JG, Bronster D, Adams DH. Incidence, imaging analysis, and early and late outcomes of stroke after cardiac valve operation. Am J Cardiol 2008;101:1472–8.
[49] Saczynski JS, Marcantonio ER, Quach L, Fong TG, Gross A, Inouye SK *et al*. Cognitive trajectories after postoperative delirium. N Engl J Med 2012;367:30–9.
[50] Aggarwal M, Khan IA. Hypertensive crisis: hypertensive emergencies and urgencies. Cardiol Clin 2006;24:135–46.
[51] Selnes OA, Gottesman RF, Grega MA, Baumgartner WA, Zeger SL, McKhann GM. Cognitive and neurologic outcomes after coronary-artery bypass surgery. N Engl J Med 2012;366:250–7.
[52] Vianna LC, Deo SH, Jensen AK, Holwerda SW, Zimmerman MC, Fadel PJ. Impaired dynamic cerebral autoregulation at rest and during isometric exercise in type 2 diabetes patients. Am J Physiol Heart Circ Physiol 2015;308:681–7.