Neuroprotective strategies with circulatory arrest in open aortic surgery – A meta-analysis

Imthiaz Manoly1, Mohsin Uzzaman2, Dimos Karangelis3, Manoj Kuduvalli4, Efstratios Georgakarakos5, Cesare Quarto6, Ramanish Ravishankar7, Fotis Mitropoulos8 and Abdul Nasir2

Abstract

Objective: Deep hypothermic circulatory arrest (DHCA) in aortic surgery is associated with morbidity and mortality despite evolving strategies. With the advent of antegrade cerebral perfusion (ACP), moderate hypothermic circulatory arrest (MHCA) was reported to have better outcomes than DHCA. There is no standardised guideline or consensus regarding the hypothermic strategies to be employed in open aortic surgery. Meta-analysis was performed comparing DHCA with MHCA + ACP in patients having aortic surgery.

Methods: A systematic review of the literature was undertaken. Any studies with DHCA versus MHCA + ACP in aortic surgeries were selected according to specific inclusion criteria and analysed to generate summative data. Statistical analysis was performed using STATS Direct. The primary outcomes were hospital mortality and post-operative stroke. Secondary outcomes were cardiopulmonary bypass time (CPB), post-operative blood transfusion, length of ICU stay, respiratory complications, renal failure and length of hospital stay. Subgroup analysis of primary outcomes for Arch surgery alone was also performed.

Results: Fifteen studies were included with a total of 5869 patients. There was significantly reduced mortality (Pooled OR = +0.64, 95% CI = +0.49 to +0.83; p = 0.0006) and stroke rate (Pooled OR = +0.62, 95% CI = +0.49 to +0.79; p < 0.001) in the MHCA group. MHCA was associated significantly with shorter CPB times, shorter duration in ICU, less pulmonary complications, and reduced rates of sepsis. There was no statistical difference between the two groups in terms of circulatory arrest times, X-Clamp times, total operation duration, transfusion requirements, renal failure and post-op hospital stay.

Conclusion: MHCA + ACP are associated with significantly better post-operative outcomes compared with DHCA for both mortality and stroke and majority of the secondary outcomes.

Keywords

Cerebral protection, aortic surgery, aortic disease, hypothermic circulatory arrest, selective antegrade cerebral protection

Introduction

Aortic arch surgery has undergone significant evolution, owing to the devotion of substantial efforts by the clinicians and laboratory researchers over the years. The long-term outcomes of open aortic surgery have been impacted by the implementation of different neuroprotective strategies. Deep hypothermic circulatory arrest (DHCA) has been the cornerstone in minimizing end organ injuries especially cerebral injury by decreasing cerebral metabolic activities. The duration and the degree of temperature to conduct safe hypothermic circulatory arrest in aortic operations were reported in observational studies.

Though supplemented with selective antegrade cerebral perfusion (SACP) and/or retrograde cerebral perfusion

1 Burjeel Medical City, Abu Dhabi, United Arab Emirates
2 Peshawar Institute of Cardiology, Peshawar, Pakistan
3 Department of Cardiac Surgery, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, Greece
4 Liverpool Heart and Chest Hospital, Liverpool, UK
5 Department of Vascular Surgery, Democritus University of Thrace, University Hospital of Alexandroupolis, Alexandroupolis, Greece
6 Royal Brompton and Harefield Hospitals, London, UK
7 University of Edinburgh, Edinburgh, UK
8 Department of Cardiac Surgery, Mitera Hospital, Athens, Greece

Corresponding author:
Dimos Karangelis, Department of Cardiac Surgery, Democritus University Hospital of Alexandroupolis, Greece.
Email: dimoskaragel@yahoo.gr
(RCP), to mitigate prolonged circulatory arrest time and the resulting neurological outcomes, DHCA still had its own limitations. The implementation of SACP also reported technical glitches of axillary cannulation, dissection of epiaortic vessels and dislodgement of atheromatous plaques. There are reports on successful conduction of moderate hypothermic circulatory arrest (MHCA) to mitigate the adverse events due to DHCA. This meta-analysis aims to compare the outcome of patients who had aortic surgeries implementing either MHCA + ACP or DHCA.

### Material and methods

#### Literature search strategy

A systematic review was conducted by applying the following two search strategies in the US National Library of Medicine – National Institutes of Health PubMed search engine:

1. (Deep(Title)) OR Moderate(Title)) OR Hypothermia(Title) OR Hypothermic(title) OR Circulatory Arrest(Title)
2. (Aortic(title) OR Arch(title) OR Ascending(title) OR Hemiarch(title))

The resulting titles and abstracts were screened for relevance, followed by evaluation of the remaining publications in their entirety.

#### Selection criteria

The meta-analysis included comparative studies in which patient cohorts underwent either DHCA or MHCA + SACP for aortic surgeries. As per the Expert Consensus published in 2013, deep hypothermia is defined as the nasopharyngeal temperature range of 14.1°C–20°C, while moderate hypothermia ranges from 20.1°C–28°C.2 This criterion was applied to include the study for meta-analysis, to standardise the results (Supplemental Table 1). In our selected studies, two (Misfeld and Halkos) measured bladder temperature while one study (Wiedemann) measured oesophageal temperature for core temperature.

Publications were excluded if they were:

- Not available in English.
- Involved animal studies.
- Pertained to literature reviews or single case reports.

The criteria were widened further by using the ‘related article’ function during the search. Additionally, a manual search was performed for publications in keeping with the above criteria. CINAHL, DARE, ACP, LILACS, SCOPUS, Google Scholar and EMBASE databases were also used to conduct the search from 1966 to 2020. This search was supplemented by a hand search of published abstracts from 1980 to 2020 in meetings of the Society of Academic and Research Surgery, Surgical Research Society, Society of Cardiothoracic Surgeons, World Congress of Cardiothoracic Surgery, the European Society of Cardiothoracic Surgeons, Society of Thoracic Surgeons (STS) and The American Association of Thoracic Surgery. Finally, the Current Controlled Trials Register, The Cochrane Database of Controlled Trials and Science Citation Index Expanded were searched. The reference lists of all articles obtained were also examined to identify additional relevant studies. Review articles were also obtained to determine other possible studies. We applied the PRISMA guidelines for meta-analysis inculcating also the principles of MOOSE guidelines.

Eligibility for study inclusion into the meta-analysis and study quality assessment was performed independently by two of the authors (IM and MU). Study data was extracted onto standard forms. Any disagreements were resolved by the senior authors. Studies were only included if they were trials in which direct comparisons were made between patients who had Moderate Hypothermic Circulatory Arrest (MHCA) versus Deep Hypothermic Circulatory Arrest (DHCA) during aortic surgery. Any unclear or missing information was obtained by contacting the authors of the individual trials. For duplicate publications, the smaller dataset was excluded.

The quality of each study was assessed by use of Newcastle-Ottawa scale, which is a nine-point scale that assigns points on the basis of the process of selection (0–4 points), comparability (0–2 points), and identification of the outcomes of study participants (0–3 points).

The primary outcome measures were peri-operative death and stroke or permanent neurological deficit (PND). Peri-operative deaths was defined as deaths occurring within the same hospital stay or within 30 days. PND was defined as stroke with/without coma as reported in the earlier reviews. Secondary outcomes were categorised into intra-operative and post-operative measures. The former included duration of surgery, cardiopulmonary bypass time, cross clamp time, and hypothermic circulatory arrest times. The latter included total intubation time, blood transfusion requirements, length of ICU stay, length of hospital stay and post-operative complications (pulmonary, renal and sepsis).

Only trials that reported at least one of the primary or secondary outcome measures were included in the meta-analysis. Subgroup analysis was also performed looking at primary outcomes of mortality and stroke after isolated aortic arch surgery which by definition, was any aortic surgery involving total arch replacement with reimplantation of branch vessels.

#### Statistical analysis

Data from the individual eligible studies were entered into a spreadsheet for further analysis. StatsDirect 2.5.7.
UK) was used to perform the statistical analysis. Weighted mean differences (WMD) were calculated for the effect size of continuous variables such as Hospital/ITU stay and CPB/X-Clamp times. Pooled odds-ratios (OR) were calculated for discrete variables such as stroke and in-hospital mortality rates.

The random-effects models (DerSimion Laird) were used to calculate the outcomes of both binary and continuous data to control any heterogeneity between the studies. Heterogeneity amongst the trials was determined by means of the Cochran Q value and quantified using the I² inconsistency test. In this study, we did not perform meta-regression or sensitivity analysis because of the small number of studies included. All p-values were 2-sided and a five percent (0.05) level was considered significant.

**Results**

The search criteria as stated in the methods section were performed. The publication selection process is illustrated in Figure 1.

Search strategies #1 and #2 described above yielded 173 and 241 results, respectively. Of the 173 results from search strategy #1, 163 were excluded on screening, two were excluded due to lack of parameters of interest and one was excluded due to overlapping cohort, leaving 7 publications for analysis. Of the 241 results from search strategy #2, 225 were excluded on screening. On further evaluation, 8 publications were excluded due to lack of parameters of interest and three were excluded due to overlapping cohort leaving 5 publications for analysis.

A further manual search was conducted which yielded 11 studies. Eight of these were duplicate studies as they were common to the search strategies #1 and #2 so were excluded. The remaining 3 studies were added to the above 12 studies yielding a total of 15 studies for our final analysis.15–29 Publication dates ranged from 2004 to 2018 (Table 1).

From these 15 studies,15–29 there were a total of 5869 patients. Of these 4051 had MHCA compared 1818 patients who had DHCA during aortic surgery. Table 2 shows the characteristics of the included trials. The aetiology of these patients were predominantly aortic dissections (acute and chronic) and a third of the patients had degenerative aneurysm.

**Primary outcomes**

**Mortality.** All fifteen studies reported on the mortality rate after aortic surgery between MHCA (n = 4051) and DHCA (n = 1818) groups. There was no statistical heterogeneity between the studies (Cochran Q = 18.7, p = 0.33; I² = 25.2%, 95%CI = 0% to 59.1%). In the random-effects model, there was a significantly reduced mortality in the MHCA group compared to the DHCA group (Pooled OR = 0.64, 95%CI = 0.49 to 0.83; p = 0.0006) (Figure 2A).

Subgroup analysis was performed on seven studies which reported mortality rate after aortic arch surgery between MHCA (n = 3008) and DHCA (n = 992). There was no statistical heterogeneity between the studies (Cochran Q = 6.87, p = 0.13; I² = 12.6%, 95%CI = 0% to 63.5%). In the random-effects model, there was a reduced mortality in the MHCA group compared to the DHCA group after arch surgery but this not significant (Pooled OR = 0.68, 95%CI = 0.45 to 1.03; p = 0.07) (Supplemental Figure 2A).

**Stroke.** All fifteen studies reported on the stroke rate after aortic surgery between MHCA (n = 4051) and DHCA (n = 1818) groups. There was no statistical heterogeneity between the studies (Cochran Q = 15.2, p = 0.36; I² = 8.1%, 95%CI = 0% to 50.6%). In the random-effects model, there was a significantly reduced stroke rate or PND in the MHCA group compared to the DHCA group (Pooled OR = 0.62, 95%CI = 0.49 to 0.79; p < 0.001) (Figure 2B).

Subgroup analysis was performed on seven studies which reported stroke rate after aortic arch surgery between MHCA (n = 3008) and DHCA (n = 992). There

**Figure 1.** Quorum chart showing study selection for meta-analysis.
Table 1. Summary of characteristics of selected studies on aortic surgeries comparing deep hypothermic circulatory arrest (DHCA) and moderate hypothermic circulatory arrest + selective antegrade cerebral perfusion (MHCA + SACP).

| Study        | Reference | Year of publication | Study period                  | Journal                 | Study type                      | MHCA + SCP | DHCA | Total | Newcastle – Ottawa Score |
|--------------|-----------|---------------------|-------------------------------|-------------------------|--------------------------------|------------|------|-------|--------------------------|
| Kaneda et al.| 16        | 2005                | Sept 1995–Sept 2003           | Scan J Surg             | Retrospective cohort study     | 51         | 17   | 68    | 7                        |
| Halkos et al.| 17        | 2009                | Jan 2004–May 2007             | J Thorac Cardiovasc Surg | Retrospective cohort study     | 196        | 66   | 262   | 8                        |
| Harrington et al.| 18      | 2004                | June 2001 January 2003        | Circulation             | Randomized Control trial       | 25         | 15   | 40    | 8                        |
| Gong et al.  | 19        | 2016                | August 2014–July 2015         | Journal of Thoracic Disease | Retrospective cohort study   | 39         | 35   | 74    | 7                        |
| Ming Ma et al.| 20       | 2015                | 2010–2013                     | Thoracic and Cardiovascular Surgeon | Retrospective cohort study | 47         | 52   | 99    | 7                        |
| Vallabhajosula et al.| 21    | 2015                | 2008–2012                     | Ann Thorac Surgery     | Retrospective cohort study     | 75         | 75   | 150   | 8                        |
| Cook et al.  | 22        | 2006                | Dec 1995–Dec 2002             | J Card Surg             | Retrospective cohort study     | 20         | 52   | 72    | 8                        |
| Tsai et al.  | 23        | 2013                | Dec 2006–May 2009             | J Thorac Cardiovasc Surg | Retrospective cohort study     | 143        | 78   | 221   | 7                        |
| Algarni et al.| 24       | 2014                | 1990–2010                     | J Thorac Cardiovasc Surg | Retrospective cohort study     | 75         | 53   | 128   | 8                        |
| Wiedemann et al.| 25      | 2013                | Apr 1987–Jan 2011             | J Thorac Cardiovasc Surg | Retrospective cohort study     | 91         | 238  | 329   | 8                        |
| Misfield et al.| 26      | 2012                | Jan 2003–Nov 2009             | Ann Thorac Surgery      | Retrospective cohort study     | 365        | 220  | 585   | 8                        |
| Minatoya et al.| 27      | 2008                | Jan 2002–2007                 | Ann Thorac Surgery      | Retrospective cohort study     | 148        | 81   | 229   | 7                        |
| Di Eusanio et al.| 28     | 2003                | Jan 1995–Sep 2001             | J Thorac Cardiovasc Surg | Retrospective cohort study     | 161        | 128  | 289   | 8                        |
| Kamenskaya et al.| 29      | 2017                | Jan 2011–Dec 2012             | J Extra Corpor Technol | Randomized Control trial       | 29         | 29   | 58    | 8                        |
| Keeling et al.| 30        | 2018                | 2000–2015                     | Ann Thorac Surgery      | Retrospective cohort study     | 2586       | 679  | 3265  | 8                        |
was no statistical heterogeneity between the studies (Cochran $Q = 6.62$, $p = 0.36$; $I^2 = 9.3\%$, 95%CI = 0% to 62.2%). In the random-effects model, there was a significantly reduced stroke rate in the MHCA group compared to the DHCA group after arch surgery (Pooled OR = +0.64, 95% CI = +0.41 to +0.98; $p = 0.04$) (Supplemental Figure 2B).

**Secondary outcomes**

The secondary outcomes measured were both peri-operative and post-operative variables, which are tabulated above (Supplemental Table 2). In general, not all the secondary outcomes were measured in all the studies mentioned and hence the difference in the total number of patients for different variables. Sepsis was analysed in only two studies and three studies mentioned about total ventilation period, total operation time and total length of hospital stay.

Of the secondary outcomes reported, MHCA + ACP was significantly better than DHCA in terms of CPB times (Pooled wmd = −23.3, 95% CI = −43.23 to −3.46; $p = 0.02$) (Figure 3A), ventilation period (Pooled wmd = −37.19, 95% CI = −58.71 to −15.67; $p = 0.0007$) (Figure 4B), total length of ICU stay (Pooled wmd = −37.64, 95% CI = −69.00 to −6.28; $p = 0.02$) (Figure 4C), sepsis (Pooled OR = 0.53, 95% CI = 0.28 to 0.99; $p < 0.046$) (Supplemental Figure 1C) and reduction in pulmonary complications including respiratory distress syndrome and lower respiratory tract infection (Pooled OR = 0.48, 95%CI = 0.35 to 0.66; $p < 0.0001$) (Supplemental Figure 1B). There was no significant difference between the two groups for peri-operative variables including total operation time (Figure 3D), cross clamp time (Figure 3C) and circulatory arrest time (Figure 3B). Post-operative variables like renal failure (Supplemental Figure 1A), blood transfusion requirement (Figure 4A) and total length of hospital stay (Figure 4D) were comparable between the two groups.

**Discussion**

There is no consensus regarding the optimal cerebral protection strategy in aortic surgery. Most high-volume aortic centres still implement DHCA alone without any CP due to its simplicity. The STS database in 2017 reported DHCA to be the most used method without any additional cerebral protection strategies. DHCA has been associated with complications including neuronal damage and increased organ dysfunction. Moderate HCA induces less inflammatory responses and hence leads to improved survival outcomes. There are

---

**Table 2. Summary of operative characteristics of selected studies on aortic surgeries comparing deep hypothermic circulatory arrest (DHCA) and moderate hypothermic circulatory arrest + selective antegrade cerebral perfusion (MHCA+SACP).**

| Study                | Total number (n) | Moderate hypothermia (n) | Deep hypothermia (n) | Aorta                        | Temperature          | ACP performed | RCP used |
|----------------------|------------------|--------------------------|----------------------|------------------------------|----------------------|---------------|----------|
| Kaneda et al.        | 68               | 51                       | 17                   | Ascending aorta/arch surgery | 28–30°C              | Yes           | No       |
| Halkos et al.        | 262              | 196                      | 66                   | Proximal aortic surgery      | 23.2 ± 4.2°C         | Yes           | No       |
| Harrington et al.    | 40               | 25                       | 15                   | Aortic arch surgery          | NS                   | Yes           | No       |
| Gong et al.          | 74               | 39                       | 35                   | Aortic arch surgery          | 20–28°C              | Yes           | No       |
| Ming Ma et al.       | 99               | 47                       | 52                   | Aortic arch surgery          | 21–26.5°C            | Yes           | No       |
| Vallabhajosula et al.| 150              | 75                       | 75                   | Transverse hemiarch          | >25°C                | Yes           | No       |
| Cook et al.          | 72               | 20                       | 52                   | Aortic arch                  | >22°C                | Yes           | No       |
| Tsai et al.          | 221              | 143                      | 78                   | Aortic arch surgery          | 22.9 ± 1.4°C         | Yes           | No       |
| Alqarni et al.       | 128              | 75                       | 53                   | Aortic root, ascending and arch surgery | 24.1 ± 1.8°C        | Mostly        | No       |
| Wiedemann et al.     | 329              | 91                       | 238                  | Ascending aorta and Arch surgery | 25°C                | Yes           | No       |
| Misfield et al.      | 585              | 365                      | 220                  | Aortic root, ascending and arch surgery | NS                   | Yes           | Yes      |
| Minatoya et al.      | 229              | 148                      | 81                   | Aortic arch surgery          | >25°C                | Yes           | No       |
| Di Eusanio et al.    | 289              | 161                      | 128                  | Ascending aorta and hemiarch | 22–26°C              | Yes           | No       |
| Kamenskaya et al.    | 58               | 29                       | 29                   | Ascending aorta and arch surgery | 23–24°C              | Yes           | No       |
| Keeling et al.       | 3265             | 2586                     | 679                  | Total aortic arch replacement | 20–28°C              | Yes           | No       |
variable reports of successful outcomes of aortic surgeries performed at different hypothermic temperatures. With the advent of SACP and RCP, finding the optimal temperature for circulatory arrest was the challenge for many aortic surgeons. There are reports of aortic surgeons implementing a warmer HCA with CP strategies and achieving better survival and neurological outcomes than without CP.

Different methods of cerebral perfusion strategies have been reported in aortic surgeries, though the most implemented ones are the SACP through axillary artery or direct arch vessel cannulation followed by RCP through SVC cannulation. Though the HCA time for aortic surgery limits the safe period to less than 60 min with deep hypothermia, the cerebral perfusion strategies with hypothermia have given the flexibility of increased safe circulatory arrest period. The SACP and RCP have got the shortcomings of being non-pulsatile and cold blood flow, though it partially maintains the cerebral circulation. Despite this, complex aortic surgeries have been performed with better results after the implementation of cerebral perfusion strategies.

The present meta-analysis demonstrated that MHCA + SACP was associated with better survival and reduced stroke rate when compared with DHCA. This is in consistence with the recent network meta-analysis done by Hameed et al. who reported lower operative mortality and post-operative stroke due to implementation of additional CP strategies compared to DHCA alone. We cannot hence attribute the better outcomes due to MHCA alone but could be due to the inclusion of cerebral perfusion as well.

On subgroup analysis on patients who had total arch replacement, we found a continued reduced mortality and stroke rate after surgery in the MHCA group compared to DHCA. However, it was only significant for stroke rates and not for mortality. Only three studies mentioned...
specifically about paraplegia which were not statistically significant between the two groups.\textsuperscript{22,25,27}

There are many factors which could attribute to better neurological outcomes in addition to cerebral perfusion. One of the major concerns during the cardiopulmonary bypass or cross clamping of the aorta is dislodging of atheromatous thrombi during cannulation or clamping of aorta. This can be alleviated with a meticulous approach of cannulation, thorough deairing and retrograde cerebral perfusion. Majority of the aortic centres monitor cerebral oxygen saturation during surgery which could indirectly measure cerebral perfusion.

Among the antegrade cerebral perfusion methods, it is still debateable whether bilateral ACP has superiority over unilateral SCP.\textsuperscript{39,40} It is reported that complete circle of Willis occurs in less than fifty percent of the observed patients.\textsuperscript{41} Our institution routinely performs bilateral ACP after opening the aortic arch and directly cannulating left common carotid artery, in addition to the right axillary artery cannulation if no contraindication. Of the studies mentioned above, implementation of bilateral or unilateral ACP in the MHCA + SACP group was according to the surgeons’ or centres’ preference.

Of the secondary outcomes analysed, MHCA group had significantly shorter CPB, total intubation time, total ICU stay and reduced pulmonary complications. There was however no significant difference between the two groups with regards to cross clamp time, HCA time, total operating time, transfusion requirements,\textsuperscript{42} total length of hospital stay and renal impairment.

One would expect increased utilisation of blood products in the DHCA group due to deep hypothermia and resultant coagulopathy. A recent study on hypothermia induced coagulopathy at different temperatures including 18°C and 24°C reported prolonged clotting time and clot formation at or below 18°C.\textsuperscript{43} Our meta-analysis however did not demonstrate this significant difference. Similarly,
the total operating times between the two groups were comparable despite longer cooling and rewarming time for the DHCA group. Renal failure was again, comparable between the two groups though the DHCA had significantly longer CPB time than the MHCA + SACP group. So though some of the secondary outcomes were significantly different between the two groups favouring the MHCA + SACP group, the complications associated with it were comparable. We could argue that most of the secondary outcomes were not consistently analysed and hence could not be validated clinically. A definite conclusion hence could not be drawn for the secondary outcomes between the two groups. One of the suggestions to overcome this incomplete analysis would be to have a multicentre, large RCT looking at specific aortic pathologies and a standard operating technique with uniform reporting of the variables. One could also look into a standard reporting registry like International Registry of Acute Aortic Dissection where most of the required variables could be analysed.

This meta-analysis has a few limitations. Except for two RCTs, majority of the studies in our meta-analysis were retrospective, observational studies, as was the norm in earlier aortic surgeries. There were also variations in arch pathologies, operating techniques across different aortic centres, differing timing of surgeries and the mode of presentation. Emergency surgeries, including aortic dissection, are essentially an independent risk factors which contributes to poorer outcomes. Thus, a true comparison could not be made in our study due to difference in aortic pathologies.

Keeling et al. compared the two HCA strategies undergoing only total arch replacement and were able to demonstrate comparable survival outcomes with MHCA. The ongoing COMMENCE trial is designed as a multicentre single-blind trial comparing mild versus moderate HCA in hemiarch surgery. We need similar studies comparing specific aortic pathology with higher level of evidence and consistent reporting to reiterate our analysis.

In conclusion, the present meta-analysis demonstrated a significant difference in the primary outcomes favouring MHCA + SACP but failed to show the mortality benefit when investigated for a specific aortic pathology. The secondary outcomes are inconsistent and infrequently reported and hence need a standard platform to measure and validate.

Declaration of conflicting interests
The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding
The authors received no financial support for the research, authorship and/or publication of this article.

Ethical approval
Not applicable.

Informed consent
Not applicable.

ORCID iDs
Imthiaz Manoly https://orcid.org/0000-0001-8768-8239
Dimos Karangelis https://orcid.org/0000-0001-7633-9949

Supplemental material
Supplemental material for this article is available online.

References
1. Griepp RB and Di Luozzo G. Hypothermia for aortic surgery. J Thorac Cardiovasc Surg. 2013; 145(Suppl): S56–S58.
2. Yun TD, Bannon PG, Bavaria J, et al. Consensus on hypothermia in aortic arch surgery. Ann Cardiothorac Surg 2013; 2: 163–168.
3. Itagaki S, Chikwe J, Sun E, et al. Impact of cerebral perfusion on outcomes of aortic surgery: the society of thoracic surgeons adult cardiac surgery database analysis. Ann Thorac Surg 2020; 109: 428–435.
4. Fan S, Li H, Wang D, et al. Effects of four major brain protection strategies during proximal aortic surgery: a systematic review and network meta-analysis. Int J Surg 2019; 63: 8–15.
5. Urbanski PP, Lenos A, Bougioukakis P, et al. Mild-to-moderate hypothermia in aortic arch surgery using circulatory arrest: a change of paradigm? Eur J Cardiothorac Surg 2012; 41: 185–191.
6. Preventza O, Price MD, Spiliotopoulos K, et al. In elective arch surgery with circulatory arrest, does the arterial cannulation site really matter? A propensity score analysis of right axillary and innominate artery cannulation. J Thorac Cardiovasc Surg 2018; 155: 1953–1960. e4.
7. Schachner T, Nagiller J, Zimmer A, et al. Technical problems and complications of axillary artery cannulation. Eur J Cardiothorac Surg 2005; 27: 634–637.
8. Ueda T, Shimizu H, Ito T, et al. Cerebral complications associated with selective perfusion of the arch vessels. Ann Thorac Surg 2000; 70: 1472–1477.
9. Shihata M, Mittal R, Senthilselvan A, et al. Selective antegrade cerebral perfusion during aortic arch surgery confers survival and neuroprotective advantages. J Thorac Cardiovasc Surg 2011; 141: 948–952.
10. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (prisma-p) 2015: elaboration and explanation. Br Med J 2015; 350: g7647.
11. Pati D and Lorusso LN. How to write a systematic review of the literature. HERD 2018; 11: 15–30.
12. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for
reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. JAMA 2000; 283: 2008–2012.
13. Wells G, Shea B, O’Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa, ON: Ottawa Hospital Research Institute; 2012.
14. Tian DH, Wan B, Bannon PG, et al. A meta-analysis of deep hypothermic circulatory arrest versus moderate hypothermic circulatory arrest with selective antegrade cerebral perfusion. Ann Cardiothorac Surg 2013; 2: 148–158.
15. Kaneda T, Saga T, Onoe M, et al. Antegrade selective cerebral perfusion during deep hypothermic circulatory arrest for elective aortic arch surgery. Scand Cardiovasc J 2005; 39: 87–90.
16. Halkos ME, Kerendi F, Myung R, et al. Selective antegrade cerebral perfusion via right axillary artery cannulation reduces morbidity and mortality after proximal aortic surgery. J Thorac Cardiovasc Surg 2009; 138: 1081–1089.
17. Misfeld M, Leontyev S, Borger MA, et al. What is the best strategy for brain protection in patients undergoing aortic arch surgery? A single center experience of 636 patients. Ann Thorac Surg 2012; 93: 1502–1508.
18. Minatoya K, Ogino H, Matsuda H, et al. Evolving selective cerebral perfusion for aortic arch replacement: high flow rate with moderate hypothermic circulatory arrest Ann Thorac Surg 2008; 86: 1827–1831.
19. Di Eusanio M, Wesselink RMJ, Morshuis WJ, et al. Deep hypothermic circulatory arrest and antegrade selective cerebral perfusion during ascending aorta-hemiarch replacement: a retrospective comparative study. J Thorac Cardiovasc Surg 2003; 125: 849–854.
20. Kamenskaya OV, Klinkova AS, Chernyavsky AM, et al. Deep hypothermic circulatory arrest vs. Antegrade cerebral perfusion in cerebral protection during the surgical treatment of chronic dissection of the ascending and arch aorta. J Extra Corpor Technol 2017; 49: 16–25.
21. Keeling WB, Tian DH, Leshnower BG, et al. Safety of moderate hypothermia with antegrade cerebral perfusion in total aortic arch replacement. Ann Thorac Surg 2018; 105: 54–61.
22. Harrington DK, Walker AS, Kaukuntla H, et al. Selective antegrade cerebral perfusion attenuates brain metabolic deficit in aortic arch surgery: a prospective randomized trial. Circulation. 2004; 110(Suppl 1): II231–II236.
23. Gong M, Ma WG, Guan XL, et al. Moderate hypothermic circulatory arrest in total arch repair for acute type A aortic dissection: clinical safety and efficacy. J Thorac Dis 2016; 8: 925–933.
24. Ma M, Liu L, Feng X, et al. Moderate hypothermic circulatory arrest with antegrade cerebral perfusion for rapid total arch replacement in acute type A aortic dissection. Thorac Cardiovasc Surg 2016; 64: 124–132.
25. Vallabhajosyula P, Jassar AS, Menon RS, et al. Moderate versus deep hypothermic circulatory arrest for elective aortic transverse hemiarch reconstruction. Ann Thorac Surg 2015; 99: 1511–1517.
26. Cook RC, Gao M, Macnab AJ, et al. Aortic arch reconstruction: safety of moderate hypothermia and antegrade cerebral perfusion during systemic circulatory arrest J Card Surg 2006; 21: 158–164.
27. Tsai JY, Pan W, Lemaire SA, et al. Moderate hypothermia during aortic arch surgery is associated with reduced risk of early mortality. J Thorac Cardiovasc Surg 2013; 146: 662–667.
28. Algamri KD, Yanagawa B, Rao V, et al. Profound hypothermia compared with moderate hypothermia in repair of acute type A aortic dissection. J Thorac Cardiovasc Surg 2014; 148: 2888–2894.
29. Wiedemann D, Kocher A, Dorfmeister M, et al. Effect of cerebral protection strategy on outcome of patients with Stanford type A aortic dissection. J Thorac Cardiovasc Surg 2013; 146: 647–655. e1.
30. Manetta F, Mullan CW and Catalano MA. Neuroprotective strategies in repair and replacement of the aortic arch. Int J Angiol 2018; 27: 98–109.
31. Englum BR, He X, Gulack BC, et al. Hypothermia and cerebral protection strategies in aortic arch surgery: a comparative effectiveness analysis from the STS adult cardiac surgery database. Eur J Cardiothorac Surg 2017; 52: 492–498.
32. Cooper WA, Duarte IG, Thouarani VH3rd, et al. Hypothermic circulatory arrest causes multisystem vascular endothelial dysfunction and apoptosis. Ann Thorac Surg. 2000; 69: 696–702; discussion 703.
33. Eggum R, Ueland T, Mollnes TE, et al. Effect of perfusion temperature on the inflammatory response during pediatric cardiac surgery. Ann Thorac Surg 2008; 85: 611–617.
34. Pacini D, Pantaleo A, di Marco L, et al. Visceral organ protection in aortic arch surgery: safety of moderate hypothermia. Eur J Cardiothorac Surg 2014; 46: 438–443.
35. Spiegelvoll D, Kai M, Tang GH, et al. Selective cerebral perfusion: a review of the evidence. J Thorac Cardiovasc Surg. 2013; 145(Suppl): S59–S62.
36. Hagl C, Ergin MA, Gall JD, et al. Neurologic outcome after ascending aorta-aortic arch operations: effect of brain protection technique in high-risk patients. J Thorac Cardiovasc Surg 2001; 121: 1107–1121.
37. Apostolakis E and Shuhaiber JH. Antegrade or retrograde cerebral perfusion as an adjunct during hypothermic circulatory arrest for aortic arch surgery. Expert Rev Cardiovasc Ther 2007; 5: 1147–1161.
38. Hameed I, Rahouma M, Khan FM, et al. Cerebral protection strategies in aortic arch surgery: a network meta-analysis. J Thorac Cardiovasc Surg. 2020; 159(1): 18–31.
39. Urbanski PP, Lenos A, Blume JC, et al. Does anatomical completeness of the circle of Willis correlate with sufficient cross-perfusion during unilateral cerebral perfusion? Eur J Cardiothorac Surg 2008; 33: 402–408.
40. Karatas A, Coban G, Cinar C, et al. Assessment of the circle of Willis with cranial tomography angiography. Med Sci Monit 2015; 21: 2647–2652.
41. Macchi C, Catini C, Federico C, et al. Magnetic resonance angiographic evaluation of circulus arteriosus cerebri (circle of Willis): a morphologic study in 100 human healthy subjects. Ital J Anat Embryol 1996; 101: 115–123.
42. Ayapdin AZ, Islamoglu F, Iyem H, et al. Experience with cerebral perfusion in total aortic arch replacement. Med Sci Monit 2002; 8: CR801–CR804.
43. Wallner B, Schenk B, Hermann M, et al. Hypothermia-associated coagulopathy: a comparison of viscoelastic monitoring, platelet function, and real time live
confocal microscopy at low blood temperatures, an in vitro experimental study. *Front Physiol* 2020; 11: 843.

44. Sun X, Yang H, Li X, et al. Randomized controlled trial of moderate hypothermia versus deep hypothermia anesthesia on brain injury during Stanford A aortic dissection surgery. *Heart Vessels* 2018; 33: 66–71.

45. Guan XL, Wang XL, Liu YY, et al. Changes in the hemostatic system of patients with acute aortic dissection undergoing aortic arch surgery. *Ann Thorac Surg* 2016; 101: 945–951.

46. Jabagi H, Wells G and Boodhwani M. COMMENCE trial (comparing hypOtherMic teMperaturEs during hemiarCh surgEry): a randomized controlled trial of mild vs moderate hypothermia on patient outcomes in aortic hemiarch surgery with anterograde cerebral perfusion. *Trials* 2019; 20: 691.