Adjunct retrograde cerebral perfusion provides superior outcomes compared with hypothermic circulatory arrest alone: A meta-analysis

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ABSTRACT

Objective: Retrograde cerebral perfusion is becoming less frequently used as a method of neuroprotection during aortic surgery. The present meta-analysis aims to compare outcomes after arch surgery with hypothermic circulatory arrest versus hypothermic circulatory arrest + retrograde cerebral perfusion.

Methods: Electronic searches were performed using 7 databases from their inception to September 2016. Relevant comparative studies that included patient groups who underwent aortic arch surgery using hypothermic circulatory arrest with continuous retrograde cerebral perfusion or hypothermic circulatory arrest alone were identified, and data were extracted by 2 independent researchers. Data were aggregated using a random-effects model per predefined clinical end points.

Results: Twenty-eight comparative studies were identified, with 2705 hypothermic circulatory arrest cases and 2817 hypothermic circulatory arrest + retrograde cerebral perfusion cases. No significant differences were seen between both groups in terms of age, gender, proportion of dissections and aneurysms, and hemiarch/total arch repair. The hypothermic circulatory arrest + retrograde cerebral perfusion group had slightly longer cardiopulmonary bypass time and lower body arrest time. Mortality was significantly increased for the hypothermic circulatory arrest cohort compared with the hypothermic circulatory arrest + retrograde cerebral perfusion cohort (odds ratio, 1.75; 95% confidence interval, 1.16-2.63; $P = .007$; $I^2 = 54\%$), but not on pooling of adjusted estimates. Stroke was also increased for the hypothermic circulatory arrest cohort (odds ratio, 1.50; 95% confidence interval, 1.07-2.10; $P = .02$; $I^2 = 29\%$). No difference in temporary neurologic deficit was identified ($P = .66$). Meta-regression found the treatment effect for mortality and stroke to be less pronounced in more contemporary series.

Conclusions: These results suggest that the addition of retrograde cerebral perfusion during aortic arch surgery may provide better outcomes than using hypothermic circulatory arrest alone, although significant confounders exist. Further robust studies are required to confirm the utility of retrograde cerebral perfusion in arch surgery. (J Thorac Cardiovasc Surg 2018;156:1339-48)

Simplified forest plot of 30-day/in-hospital mortality with HCA versus HCA + RCP.

Central Message

In comparison with straight HCA, adjunctive RCP may reduce PNDs and possibly mortality, although significant confounders exist in the literature.

Perspective

Despite waning practice of RCP, existing clinical evidence suggests that it may offer better outcomes than HCA alone, although more robust and modern clinical evidence is required to validate this. Further high-level clinical studies are required to investigate technical parameters of RCP to minimize neurologic complications.

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See Editorial page 1337.

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Abbreviations and Acronyms

ACP = antegrade cerebral perfusion
 CI = confidence interval
 CPB = cardiopulmonary bypass
 HCA = hypothermic circulatory arrest
 OR = odds ratio
 PND = permanent neurologic deficit
 RCP = retrograde cerebral perfusion
 TND = temporary neurologic deficit

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The application of retrograde cerebral perfusion (RCP) as an adjunct to hypothermic circulatory arrest (HCA) has diminished significantly in recent years.^{1,2} First popularized in 1990, RCP was theorized to be able to supply cerebral parenchyma with metabolites and wash away catabolites, to be able to flush embolic debris downstream away from the brain, and to also offer targeted topical cooling.^{3,4} However, animal studies performed in the decade since have largely discounted the ability for RCP to adequately supply metabolites to the brain. Despite this, clinical studies on the benefits of RCP have been equivocal, even positive, with some centers still practicing this technique today with good results, particularly in acute dissections.^{5,6}

Numerous studies and meta-analyses have been published to date that examine the efficacy and outcomes of RCP compared with antegrade cerebral perfusion (ACP). However, no such meta-analysis exists comparing HCA alone with supplemental RCP (HCA + RCP). While understanding the slightly differing underlying patient populations (HCA may typically be used in shorter, less complex cases), the present analysis aims to evaluate the benefits of adjunct RCP on postoperative outcomes.

MATERIALS AND METHODS

Literature Search

To compare the outcomes of patients who underwent aortic arch surgery with HCA alone or in conjunction with RCP, electronic searches were performed using Ovid Medline, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Review of Effectiveness, and PubMed from their dates of inception to September 2016. To achieve maximum sensitivity, we combined the terms (“retrograde cerebral perfusion” or “RCP”) AND (“hypothermic circulatory arrest” OR “HCA”), as key terms or MeSH headings. The search strategy adopted is in

accordance with the Meta-analysis of Observational Studies in Epidemiology and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.^{7,8} All identified articles were systematically evaluated by 2 independent researchers according to the inclusion/exclusion criteria.

Inclusion/Exclusion Criteria

Eligible studies for the present meta-analysis included those in which adult patients undergoing surgery on the thoracic aortic arch received HCA or HCA with RCP as the primary neuroprotection strategy. No limitation was placed on the temperature of circulatory arrest. Studies that used intermittent RCP or a brief period of RCP to flush the brain vasculature were excluded. Studies that did not provide specific primary outcomes or with less than 10 patients in either cohort were excluded, as were those investigating pediatric populations or animal studies. All publications were limited to English. Letters, editorials, case reports, conference abstracts, and review articles were excluded. Where hospitals have published duplicating trials, only the most up-to-date or comprehensive study was included. It is acknowledged that patient selection varied among institutions and between time periods.

Quality Assessment and Outcome Measures

Quality assessment was performed using a modified schema based on a quality appraisal tool for case series developed by the Institute of Health Economics in Canada.⁹ In short, studies were scored based on 6 main domains: clarity of objective, characteristics of the study population, description of the intervention, adequate outcome measures, suitable statistical analysis, and appropriate results/conclusions (Table E1). Each article was scored out of 13, with 12 to 13 deemed as high quality, 9 to 11 deemed as medium-quality, and 8 or less deemed as low-quality.

Primary outcomes of interest included 30-day/in-hospital mortality and permanent neurologic deficit (PND). Because of the variability in the definitions of temporary neurologic deficit (TND), this was recorded as a secondary outcome of interest. Other secondary outcomes included incidence of acute kidney injury, spinal cord injury, reoperation for bleeding, and intensive care unit and in-hospital stay. Outcome measures were only analyzed if at least 50% of studies reported such results.

All data were extracted independently from abstracts, texts, figures, and tables by 2 independent researchers (D.H.T., J.W.) into Microsoft Excel (Microsoft Corp, Redmond, Wash). Discrepancies between the 2 researchers were resolved by consensus.

Statistical Method

Meta-analysis of proportions or means was performed to calculate pooled results. Median and interquartile range were converted to mean $\pm$ standard deviation using the techniques of Wan and colleagues.¹⁰ To account for variations in surgical practice and patient selection, a random-effect Mantel-Haenszel model was used. Odds ratio (OR) was used as a summary statistic. I^2 statistic was used to estimate the percentage of total variation across studies, due to heterogeneity rather than chance. An I^2 value of greater than 50% was considered substantial heterogeneity. If there was substantial heterogeneity, the possible clinical and methodological reasons for this were explored qualitatively. Adjusted estimates were extracted from multivariable regression analysis or calculated if it was not presented because of nonsignificance on adjustment. The median year of patient enrollment was used in univariable meta-regression to determine whether temporal variations was a potential source of heterogeneity.

All statistical analysis was done in Review Manager version (version 5.3, Cochrane Collaboration, Oxford, United Kingdom), Comprehensive Meta-Analysis (version 3.3, Biostat Inc, Englewood, NJ), and R (version 3.4.3, R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Quality of Studies

After removal of duplicate records, 902 references remained for review. After excluding irrelevant articles, 137 articles were retrieved for further evaluation. Of these, 28 comparative studies were identified for detailed analysis. Manual searches of reference lists did not identify any other relevant studies. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart of the literature search is presented in [Figure E1](#).

Of the 28 included studies, all but 2 were observational series ([Table E2](#)). Studies ranged from 20 to 1193 patients (median, 101; interquartile range, 50-268). Five studies included only emergency cases, whereas 3 were entirely elective. The remaining 20 studies were of mixed population. Six studies were deemed high quality, 17 were deemed medium quality, and 5 studies were deemed poor quality.

Demographic Details

Overall, 5522 patients were included in the present analysis, with 2705 HCA cases and 2817 HCA + RCP cases. No significant differences were seen in terms of age, gender, proportion of acute dissections or aneurysms, coronary artery graft surgery, and hemiarch repair between patients who received HCA only or those with HCA + RCP, but these covariate data were not reported by all studies ([Table 1](#) and [Table E3](#)). There were more total arch replacements in the HCA + RCP cohort (12.1% vs 16.2%, $P < .04$) ([Table E4](#)). In all studies, the circulatory arrest temperature target was the same between both cohorts or only varied at most by 2°C. Cardiopulmonary bypass (CPB) time was slightly longer for the HCA + RCP cohort (177 vs 188 minutes, $P = .03$, $I^2 = 59\%$), as was the duration of lower body circulatory arrest (30 vs 34 minutes, $P = .02$, $I^2 = 84\%$). Insufficient information was available regarding other patient comorbidities and cannulation sites.

Clinical Outcomes

Overall, mortality was significantly higher in patients who received HCA as the primary neuroprotection method

compared with HCA + RCP (9.8% vs 15.8%; OR, 1.75; 95% confidence interval [CI], 1.16-2.63; $P = .007$; $I^2 = 54\%$) ([Figure 1](#) and [Table E5](#)). No difference in mortality was seen among acute dissection studies (OR, 1.36; 95% CI, 0.87-2.11; $P = .18$, $I^2 = 13\%$). When low-quality studies were excluded from the analysis, HCA + RCP remained significantly superior to HCA alone in terms of mortality (OR, 1.69; 95% CI, 1.03-2.77; $P = .04$; $I^2 = 61\%$).

Likewise, a significant increase in PND was also seen overall with the HCA cohort (6.5% vs 10.9%; OR, 1.50; 95% CI, 1.07-2.10; $P = .02$; $I^2 = 29\%$) ([Figure 2](#)) compared with HCA + RCP alone, but not in acute dissection studies (OR, 1.42; 95% CI, 0.54-3.70; $P = .47$, $I^2 = 62\%$). When only medium-/high-quality studies were included, no significant difference was seen between the 2 groups (OR, 1.37; 95% CI, 0.97-1.95; $P = .07$; $I^2 = 26\%$).

No significant difference was evident for TND between the HCA and HCA + RCP cohorts (7.7% vs 10.5%; OR, 0.85; 95% CI, 0.42-1.75; $P = .66$; $I^2 = 67\%$) ([Figure 3](#)) in the 17 studies that reported such data. The remaining secondary outcomes of interest, including reoperation for bleeding (reported in 9 studies), incidence of acute kidney injury (8 studies), spinal cord injury (1 study), intensive care unit length of stay (6 studies), and hospital length of stay (8 studies), were not sufficiently reported and thus not analyzed.

Pooled adjusted OR for mortality with HCA compared with HCA + ACP from 7 studies was 1.11 (95% CI, 0.62-1.97; $P = .72$; $I^2 = 42\%$) ([Figure 4](#)). In 5 studies, unadjusted results were used because multivariable regression did not find brain perfusion to be a significant predictor,¹¹⁻¹⁵ whereas the remaining 2 studies were randomized controlled trials.^{16,17}

Pooled adjusted OR for stroke with HCA compared with HCA + ACP from 9 studies was 1.72 (95% CI, 1.21-2.43; $P = .002$; $I^2 = 5\%$) ([Figure 5](#)). Univariable results from 6 studies were used because they did not identify RCP to be significant on multivariable regression.^{5,11-14,18} The

TABLE 1. Demographics details of overall cohort

	HCA	HCA + RCP	Studies
Age	60.5 (58.1-62.8)	61.5 (57.6-65.4)	14 studies
Male gender	65.5% (61.8-69.0)	62.5% (57.7-67.1)	12 studies
Dissection	53.9% (33.8-72.8)	54.8% (31.3-76.3)	15 studies
Aneurysm	54.8% (31.3-76.3)	31.4% (16.0-52.4)	12 studies
Hemiarch	70.7% (54.6-82.9)	67.2% (52.5-79.1)	10 studies
Total arch	12.1% (7.2-19.4)	16.2% (9.0-27.6)	12 studies
CPB time (min)	177 (161-193)	188 (176-200)	14 studies
Crossclamp time (min)	102 (91-114)	113 (104-123)	8 studies
Circulatory arrest time (min)	30 (26-34)	34 (30-39)	16 studies

Records after duplicates removed (n = 902). HCA, Hypothermic circulatory arrest; RCP, retrograde cerebral perfusion; CPB, cardiopulmonary bypass.

FIGURE 1. Forest plot of the OR of 30-day/in-hospital mortality after aortic arch surgery with HCA alone versus HCA with RCP (HCA + RCP). The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as a fraction of the total number treated are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *HCA*, Hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion; *CI*, confidence interval; *RCT*, randomized control trial.

FIGURE 2. Forest plot of the OR of PND after aortic arch surgery with HCA alone versus HCA with RCP (HCA + RCP). The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as a fraction of the total number treated are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *HCA*, Hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion; *CI*, confidence interval; *RCT*, randomized control trial.

FIGURE 3. Forest plot of the OR of TND after aortic arch surgery with HCA alone versus HCA with RCP (HCA + RCP). The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as a fraction of the total number treated are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *HCA*, Hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion; *CI*, confidence interval; *RCT*, randomized control trial.

remaining studies provided adjusted estimates¹⁵ or were randomized controlled trials.^{16,17}

The median year of patient recruitment was found to be significant on univariable meta-regression for mortality ($R^2 = 0.32$, β -coefficient = -0.08 , $P = .049$) (Figure E2) and PND ($R^2 = 1.0$, β -coefficient = -0.09 , $P = .001$) (Figure E3), suggesting that the effect of RCP was more pronounced in historic series, and that this

temporal variation fully explains the between-study variance for PND.

Publication Bias

No publication bias was seen when examined for mortality (Begg's P value = .310, Egger's P value = .476) or PND (Begg's P value = .243, Egger's P value = .101). No asymmetry was identified on funnel plots.

FIGURE 4. Forest plot of the adjusted OR of mortality after aortic arch surgery with HCA alone versus HCA with RCP (HCA + RCP). The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as a fraction of the total number treated are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. SE, Standard error; CI, confidence interval; RCT, randomized control trial; HCA, hypothermic circulatory arrest; RCP, retrograde cerebral perfusion.

DISCUSSION

The routine use of RCP has decreased significantly over the past 2 decades, driven by mediocre physiologic and animal studies and the growing acceptance of ACP.^{1,2} In particular, it has been shown in porcine models, using tracking of fluorescent microspheres, that only 0.01% of perfusate flow transits through the brain parenchyma itself, with the majority being sequestered or bypassed through nonbrain capillaries.¹⁹ Similar findings were reported in other animal studies with magnetic resonance perfusion scans and intravital microscopy,^{20,21} demonstrating the inadequacy of RCP in providing sufficient metabolites to cortical tissue. Despite this, canine and porcine models have also revealed that although not ideal, RCP does indeed provide superior metabolic support compared with HCA alone, as measured through lactate and adenosine triphosphate elimination,^{22,23} with similar superior outcomes also seen in histologic studies^{20,24} and animal studies.²⁵

The primary concern for RCP has been the risk of cerebral edema due to hyperperfusion. As RCP perfusion pressure increases, a corresponding increase in cerebral edema has been identified in animals.^{22,25} Clinically, however, Ganzel and colleagues²⁶ have shown that with extensive intraoperative neurophysiologic monitoring, RCP flow can be safely titrated and cerebral edema avoided. Indeed, in a large propensity-matched analysis of 1141 patient-pairs from the Japanese Adult Cardiovascular Database, temporary neurologic deficit was similar between RCP and the more commonly accepted method of ACP (4.4% vs 4.1%, $P = .756$).²⁷ Comparable findings were reported in a recent large meta-analysis comparing ACP and RCP (incidence of TND for RCP vs ACP: 8.7% vs 7.5%; $P = .275$), suggesting that RCP does not significantly increase adverse outcomes compared with alternative cerebral perfusion methods.²⁸ The addition of RCP also has been shown to provide superior outcomes compared with HCA alone in the Society of Thoracic Surgeons Adult Cardiac Surgery Database.²⁹

FIGURE 5. Forest plot of the adjusted OR of PND after aortic arch surgery with HCA alone versus HCA with RCP (HCA + RCP). The estimate of the OR of each study corresponds to the middle of the *squares*, and the *horizontal line* shows the 95% CI. On each line, the numbers of events as a fraction of the total number treated are shown for both treatment groups. For each subgroup, the sum of the statistics, along with the summary OR, is represented by the middle of the *solid diamonds*. A test of heterogeneity between the trials within a subgroup is given below the summary statistics. *SE*, Standard error; *CI*, confidence interval; *RCT*, randomized control trial; *HCA*, hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion.

Clinically, patients receiving HCA + RCP have been found to have reduced mortality and PND, with excellent results reported in experienced centers. In a series of 1002 ascending and transverse aortic arches repaired under HCA + RCP, Safi and colleagues⁵ reported a mortality rate of 8.6% and a stroke rate of 2.8%. Results from Coselli and LeMaire³⁰ found mortality and stroke rates of 3.4% and 2.4%, respectively, in 290 patients receiving proximal aortic repair compared with 14.8% and 6.5%, respectively, seen in 189 patients receiving HCA and RCP alone.³⁰ In the present meta-analysis, mortality was significantly reduced for the HCA + RCP cohort compared with HCA alone (8.7% vs 14.0%, $P = .007$), despite a trend for slightly greater proportion of dissection cases and total arch replacements in the HCA + RCP group. However, this result was not confirmed when only adjusted estimates were considered. Furthermore, in most of the included studies, RCP was an historical control with historic perioperative

management strategies, having been supplanted by ACP. Of note, stroke was nearly halved in those receiving HCA + RCP (5.4% vs 10.1%, $P = .02$), although this became nonsignificant when low-quality studies were excluded. This significance was retained when only adjusted estimates were included. Although it was not possible to analyze the underlying risk factors without evaluating the raw data, these results demonstrate sufficient equipoise to conduct further research into the benefit of RCP. It is also unclear from this review the precise reason why HCA + RCP has superior outcomes compared with HCA alone, although several explanations can be postulated on the basis of the available literature. First, animal studies using microspheres have confirmed the ability for RCP to flush particulate and gaseous emboli from the arterial tree, thereby reducing embolic load and the risk of stroke.^{31,32} Second, RCP offers more consistent and continuous cerebral cooling. Finally, although RCP is not able to

adequately fulfill cerebral metabolic demand, its limited flow can aid in removing neurotoxic metabolites.

Study Limitations

The findings of this review are limited by several shortcomings. First, there was insufficient information available regarding the underlying patient population, particularly with regard to patient risk factors and indications for surgery. Of note, it was also not possible to evaluate the impact of adjunctive RCP on varying durations of circulatory arrest. Second, the patient population was heterogeneous, with all but 3 of the included studies retrospective uncontrolled case series. There is likely hidden bias that cannot be accounted for in the present analysis. Third, the lack of consensus definition on PND and TND limits the analysis and comparison of these important outcome measures. In addition, as RCP has been more recently supplanted by ACP as the preferred adjunct cerebral perfusion route, in all but a minority of centers RCP data were from an historical era, therefore confounding analysis because of temporal improvements in patient care. Indeed, meta-regression has found that the median year of patient enrollment significantly contributed to the heterogeneities in mortality and PND results, with more pronounced treatment effects favoring RCP in earlier years. Finally, no clear patient selection criteria were presented in the studies, with disparity seen in the number of patients in several studies. Although this analysis focused on comparative studies in an attempt to standardize general surgical and postoperative care, biases in patient selection cannot be ruled out.

CONCLUSIONS

Despite the declining practice of RCP, there may remain a valid role for it within aortic arch surgery. In comparison with straight HCA, adjunctive RCP may reduce mortality and permanent neurologic deficits, with comparable incidence of TNDs. However, these results should be interpreted with caution given the heterogeneity of the source data, potential sources for unaccounted bias, and temporal evolution in surgical treatment. Further high-level clinical studies are required to validate the role of adjunctive RCP and investigate technical parameters of RCP to minimize neurologic complications.

Conflict of Interest Statement

Authors have nothing to disclose with regard to commercial support.

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Key Words: retrograde cerebral perfusion, hypothermic circulatory arrest, aortic arch surgery, meta-analysis

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ORIGINAL SUBMISSION: Fluctuations in Spinal Cord Perfusion Pressure: A Harbinger of Delayed Paraplegia after Thoracoabdominal Aortic Repair. Harleen K. Sandhu. *Semin Thorac Surg* 2017;451-459.

Editorial Commentary: Keep Alert Eyes on Delayed Paraplegia. Kenji Minatoya. *Semin Thorac Surg* 2017;460-461.

Editorial Commentary: Problem Delayed Does Not Mean Solution Denied. Joseph S. Coselli. *Semin Thorac Surg* 2017;462-463.

ORIGINAL SUBMISSION: Awake Thoracic Endovascular Aneurysm Repair for Aortic Rupture: A Case Series. Jessica Forcillo. *Semin Thorac Surg* 2018;36-39.

Editorial Commentary: Awake TEVAR for Ruptured Thoracic Aneurysms: Less is More? Akiko Tanaka. *Semin Thorac Surg* 2018;40-41.

FIGURE E1. PRISMA flow chart of literature search for meta-analysis of HCA versus HCA with RCP during aortic arch surgery. *HCA*, Hypothermic circulatory arrest; *RCP*, retrograde cerebral perfusion.

FIGURE E2. Meta-regression of the median year of patient enrollment against mortality for HCA versus HCA + RCP. *Thick line* represents regression line; *curved line* represents 95% CI. *Circles* represent studies with their sizes proportional to the study sample size.

FIGURE E3. Meta-regression of the median year of patient enrollment against PND for HCA versus HCA + RCP. *Thick line* represents regression line; *curved line* represents 95% CI. *Circles* represent studies with their sizes proportional to the study sample size.

TABLE E1. Modified quality assessment schema, based on Institute of Health Economics (Alberta, Canada) Quality Appraisal Tool for Case Series

Criteria
1. Is the hypothesis/aim/objective of the study clearly stated in the abstract, introduction, or methods section?
2. Are the characteristics of the participants included in the study described?
3. Were the cases collected in more than 1 center?
4. Are the eligibility criteria (inclusion and exclusion criteria) to entry the study explicit and appropriate?
5. Were participants recruited consecutively?
6. Was the intervention clearly described in the study?
7. Are the outcome measures clearly defined in the introduction or methods section?
8. Were relevant outcomes appropriately measured with objective or subjective methods?
9. Were the statistical tests used to assess the relevant outcomes appropriate?
10. Was the length of follow-up reported?
11. Was the loss to follow-up reported?
12. Are adverse events reported?
13. Are the conclusions of the study supported by results?

One point is given for each question.

TABLE E2. Summary of included studies

Author	Year published	Year of study	Hospital	HCA	HCA + RCP	Study type	Urgency of operation
Svensson	2001	1996-1999	Lahey Clinic, Burlington, Tufts University, USA	10	10	RCT	Elective
Neri	2004	1999-2003	University of Siena, Italy	23	19	Prospective	Elective
Mishra	2009	NA	All India Institute of Medical Sciences, India	14	52	Retrospective	Elective
Sinatra	2001	1992-1998	University of Rome "La Sapienza," Italy	44	18	Retrospective	Emergency
Zierer	2007	1984-2005	Washington University School of Medicine, USA	69	56	Retrospective	Emergency
Forteza	2009	1990-2008	Hospital Universitario 12 de Octubre, Spain	32	26	Retrospective	Emergency
Wiedemann	2013	1987-2011	Vienna Medical University, Austria	116	122	Retrospective	Emergency
Stamou	2016	2000-2010	5 centers, USA	184	55	Retrospective	Emergency
Bavaria	1995	1987-1994	University of Pennsylvania, USA	24	14	Retrospective	Mixed
Coselli	1997	1987-1996	Baylor College of Medicine, USA	189	290	Retrospective	Mixed
Caimmi	1998	1989-1994	University of Turin, Italy	43	10	Retrospective	Mixed
Wong	1999	1991-1998	Queen Elizabeth Medical Centre, UK	34	96	Retrospective	Mixed
Hagl	2001	1986-1999	Mount Sinai School of Medicine, USA	588	43	Retrospective	Mixed
LeMaire	2001	NA	Baylor College of Medicine, USA	12	25	Prospective	Mixed
Dong	2002	NA	Beijing Anzhen Hospital, China	15	50	Retrospective	Mixed
Bonser	2002	NA	Queen Elizabeth Medical Centre, UK	21	21	RCT	Mixed
Matalanis	2003	1996-2000	Austin and Repatriation Medical Centre, Australia	14	23	Retrospective	Mixed
Schachner	2004	1980-2002	Medical University Innsbruck, Austria	110	25	Retrospective	Mixed
Guan	2004	1982-2001	Beijing Anzhen Hospital, China	17	61	Retrospective	Mixed
Müller	2004	1999-2001	University Hospital Frankfurt/Main, Germany	12	22	Retrospective	Mixed
Chong	2004	1999-2012	Singapore General Hospital and National University Hospital, Singapore	15	44	Retrospective	Mixed
Sundt	2008	1993-2007	Mayo Clinic Rochester, USA	220	53	Retrospective	Mixed
Apaydin	2009	1993-2006	Ege University Medical School, Turkey	48	94	Retrospective	Mixed
Safi	2011	1991-2010	Memorial Hermann Heart and Vascular Institute, USA	191	1002	Retrospective	Mixed
Misfeld	2012	2003-2009	Leipzig Heart Center, Germany	220	51	Retrospective	Mixed
Di Mauro	2013	1988-2009	Prince Sultan Cardiac Centre, Riyadh, Saudi Arabia	69	198	Retrospective	Mixed
Kaneko	2014	2002-2012	Brigham and Women's Hospital, USA	276	77	Retrospective	Mixed
Okada	2015	1986-2008	Nagoya University Graduate School of Medicine, Japan	95	260	Retrospective	Mixed
Overall				2705	2817		

HCA, Hypothermic circulatory arrest; RCP, retrograde cerebral perfusion; RCT, randomized controlled trial; NA, not available.

TABLE E3. Demographics of included patients

First author	Age		Male		Dissection		Aneurysm	
	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP
Svensson	NA	NA	NA	NA	0	0	NA	NA
Neri	68 ± 3	70 ± 4	15 (65)	14 (74)	0	0	17 (74)	14 (74)
Mishra	NA	NA	NA	NA	0	0	NA	NA
Sinatra	59 ± 14	62 ± 11.2	33 (75)	11 (61)	44 (100)	18 (100)	0 (0)	0 (0)
Zierer	63 ± 15	63 ± 15	45 (65)	31 (55)	69 (100)	56 (100)	0 (0)	0 (0)
Forteza	NA	NA	NA	NA	32 (100)	26 (100)	0 (0)	0 (0)
Wiedemann	60 ± 11*	56 ± 12*	82 (71)	75 (61)	116 (100)	122 (100)	0 (0)	0 (0)
Stamou	59 ± 11*	62 ± 15*	125 (68)	38 (69)	184 (100)	55 (100)	0 (0)	0 (0)
Bavaria	NA	NA	NA	NA	14 (58)	9 (64)	10 (42)	5 (36)
Coselli	NA	NA	NA	NA	NA	NA	NA	NA
Caimmi	NA	NA	NA	NA	NA	NA	NA	NA
Wong	NA	NA	NA	NA	NA	NA	NA	NA
Hagl	NA	NA	NA	NA	NA	NA	NA	NA
LeMaire	59 ± 12	63 ± 12	10 (83)	16 (64)	NA	NA	NA	NA
Dong	50 ± 12	49 ± 11	NA	NA	NA	NA	NA	NA
Bonser	54 ± 10*	58 ± 15*	12 (57)	12 (57)	3 (14)	2 (10)	16 (76)	14 (67)
Matalanis	64 ± 10	63 ± 11	12 (86)	16 (70)	6 (43)	17 (74)	NA	NA
Schachner	NA	NA	NA	NA	NA	NA	NA	NA
Guan	NA	NA	NA	NA	NA	NA	NA	NA
Müller	62 ± 11	64 ± 11	5 (42)	11 (50)	8 (67)	11 (50)	4 (33)	11 (50)
Chong	NA	NA	NA	NA	NA	NA	NA	NA
Sundt	65 ± 13	71 ± 8	131 (60)	26 (49)	35 (16)	12 (23)	134 (61)	28 (53)
Apaydin	56 ± 12	54 ± 12	NA	NA	NA	NA	NA	NA
Safi	NA	NA	NA	NA	NA	NA	NA	NA
Misfeld	62 ± 15	62 ± 14	136 (62)	38 (75)	71 (32)	14 (27)	143 (65)	36 (71)
Di Mauro	NA	NA	NA	NA	NA	NA	NA	NA
Kaneko	61 ± 14	64 ± 13	185 (67)	52 (68)	26 (9)	10 (13)	245 (89)	66 (86)
Okada	NA	NA	NA	NA	NA	NA	NA	NA
Average	60.5 (58.1-62.8)	61.5 (57.6-65.4)	65.5% (61.8-69.0)	62.5% (57.7-67.1)	53.9% (33.8-72.8)	54.8% (31.3-76.3)	33.6% (18.9-52.3)	31.4% (16.0-52.4)

HCA, Hypothermic circulatory arrest; RCP, retrograde cerebral perfusion; NA, not available. *Mean and standard deviation calculated from median/interquartile range using techniques of Wan and colleagues.¹⁰

TABLE E4. Summary of surgical procedures

Author	CABG		Hemiarch		Total arch		Circulatory arrest temperature		Temperature measure site
	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP	
Svensson	3 (30)	2 (20)	NA	NA	NA	NA	NA	NA	NA
Neri	NA	NA	14 (61)	10 (53)	9 (39)	9 (47)	19 ± 3	21 ± 1	Nasopharyngeal
Mishra	NA	NA	NA	NA	NA	NA	18	18	Nasopharyngeal
Sinatra	NA	NA	NA	NA	9 (20)	6 (33)	17	17	Rectal
Zierer	24 (35)	7 (13)	32 (46)	25 (45)	0 (0)	0 (0)	17 ± 3	19 ± 3	Bladder
Forteza	NA	NA	NA	NA	NA	NA	18	18	Bladder
Wiedemann	11 (9)	10 (8)	NA	NA	0 (0)	3 (2)	18	18	Esophageal
Stamou	NA	NA	102 (55)	37 (67)	9 (5)	3 (5)	19 ± 4*	19 ± 6*	NA
Bavaria	NA	NA	NA	NA	5 (21)	3 (21)	16	15	Nasopharyngeal
Coselli	NA	NA	NA	NA	NA	NA	14.5	14.5	Nasopharyngeal
Caimmi	NA	NA	NA	NA	NA	NA	18	18	Rectal
Wong	NA	NA	NA	NA	NA	NA	15	15	Nasopharyngeal
Hagl	NA	NA	NA	NA	NA	NA	10-13	10-13	Esophageal
LeMaire	NA	NA	9 (75)	17 (68)	3 (25)	8 (32)	11 ± 3	11 ± 2	Nasopharyngeal
Dong	NA	NA	NA	NA	NA	NA	18	18	Nasopharyngeal
Bonser	3 (14)	0 (0)	5 (24)	5 (24)	3 (14)	3 (14)	15	15	Nasopharyngeal
Matalanis	3 (21)	8 (35)	6 (43)	15 (65)	1 (7)	6 (26)	19 ± 2	19 ± 1	NA
Schachner	NA	NA	NA	NA	NA	NA	18	18	Rectal
Guan	NA	NA	NA	NA	NA	NA	18	18	Nasopharyngeal
Müller	1 (8)	6 (27)	NA	NA	NA	NA	20 ± 2	20 ± 2	Rectal
Chong	NA	NA	NA	NA	NA	NA	NA	NA	Nasopharyngeal
Sundt	62 (28)	12 (23)	191 (87)	32 (60)	29 (13)	21 (40)	16-18	16-18	Nasopharyngeal
Apaydin	NA	NA	48 (100)	94 (100)	NA	NA	16	16	Rectal
Safi	NA	NA	NA	NA	NA	NA	15-20	15-20	Nasopharyngeal
Misfeld	51 (23)	12 (24)	174 (79)	42 (82)	46 (21)	9 (18)	22 ± 2	23 ± 3	NA
Di Mauro	NA	NA	NA	NA	NA	NA	20	20	Nasopharyngeal
Kaneko	59 (21)	15 (19)	276 (100)	77 (100)	0 (0)	0 (0)	18.0 ± 0*	18 ± 0*	Nasopharyngeal
Okada	NA	NA	NA	NA	NA	NA	18-20	18-20	Rectal
Average	22.1% (17.2-28.0)	18.6% (13.1-25.8)	70.7% (54.6-82.9)	67.2% (52.5-79.1)	12.1% (7.2-19.4)	16.2% (9.0-27.6)			

CABG, Coronary artery bypass grafting; HCA, hypothermic circulatory arrest; RCP, retrograde cerebral perfusion; NA, not available. *Mean and standard deviation calculated from median/interquartile range using techniques of Wan and colleagues.¹⁰

TABLE E5. Overall clinical outcomes

Author	CPB time		Crossclamp time		Circulatory arrest time		Mortality		Stroke		TND	
	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP	HCA	HCA + RCP
Svensson	NA	NA	NA	NA	NA	NA	0 (0)	0 (0)	0 (0)	0 (0)	NA	NA
Neri	132 ± 40	172 ± 48	NA	NA	NA	NA	0 (0)	0 (0)	2 (9)	0 (0)	5 (22)	4 (21)
Mishra	NA	NA	NA	NA	NA	NA	1 (7)	4 (8)	4 (29)	0 (0)	NA	NA
Sinatra	210 ± 89	219 ± 77	NA	NA	51 ± 32	56 ± 25	16 (36)	3 (17)	11 (25)	0 (0)	5 (11)	2 (11)
Zierer	202 ± 72	194 ± 65	129 ± 54	105 ± 50	36 ± 15	39 ± 15	13 (19)	11 (20)	4 (6)	1 (2)	19 (28)	5 (9)
Forteza	NA	NA	NA	NA	NA	NA	4 (13)	6 (23)	2 (6)	3 (12)	3 (9)	5 (19)
Wiedemann	177 ± 42*	198 ± 47*	107 ± 24*	114 ± 28*	36 ± 13*	30 ± 12*	30 (26)	20 (16)	27 (23)	15 (12)	1 (1)	0 (0)
Stamou	192 ± 89*	207 ± 88*	NA	NA	17 ± 24*	36 ± 14*	35 (19)	8 (15)	26 (14)	12 (22)	NA	NA
Bavaria	NA	NA	NA	NA	NA	NA	9 (38)	1 (7)	11 (46)	0 (0)	NA	NA
Coselli	NA	NA	NA	NA	NA	NA	32 (17)	10 (3)	12 (6)	7 (2)	NA	NA
Caimmi	NA	NA	NA	NA	NA	NA	8 (19)	1 (10)	1 (2)	0 (0)	2 (5)	1 (10)
Wong	NA	NA	NA	NA	NA	NA	8 (24)	14 (15)	2 (6)	7 (7)	NA	NA
Hagl	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	34 (6)	13 (30)
LeMaire	135 ± 20	125 ± 48	NA	NA	35 ± 14	34 ± 13	NA	NA	0 (0)	3 (12)	NA	NA
Dong	204 ± 57	220 ± 66	82 ± 32	141 ± 49	37 ± 19	46 ± 17	5 (33)	1 (2)	3 (20)	1 (2)	NA	NA
Bonser	145 ± 24	153 ± 36	NA	NA	32 ± 9	27 ± 12	1 (5)	2 (10)	1 (5)	0 (0)	0 (0)	2 (10)
Matalanis	196 ± 60	194 ± 35	81 ± 68	106 ± 33	25 ± 12	37 ± 19	1 (7)	0 (0)	0 (0)	1 (4)	1 (7)	0 (0)
Schachner	NA	NA	NA	NA	32 ± 10*	39 ± 16*	NA	NA	7 (6)	1 (4)	NA	NA
Guan	NA	NA	NA	NA	36 ± 19	43 ± 18	3 (18)	1 (2)	3 (18)	2 (3)	3 (18)	2 (3)
Müller	188 ± 64	195 ± 75	70 ± 27	106 ± 47	23 ± 13	23 ± 11	2 (17)	2 (9)	0 (0)	1 (5)	NA	NA
Chong	NA	NA	NA	NA	NA	NA	NA	NA	5 (33)	12 (27)	NA	NA
Sundt	141 ± 54	176 ± 65	NA	NA	27 ± 14	33 ± 13	16 (7)	9 (17)	20 (9)	5 (9)	NA	NA
Apaydin	198 ± 48	183 ± 41	106 ± 35	98 ± 30	34 ± 9	40 ± 11	NA	NA	2 (4)	1 (1)	3 (6)	12 (13)
Safi	NA	NA	NA	NA	NA	NA	25 (13)	87 (9)	8 (4)	28 (3)	NA	NA
Misfeld	186 ± 65	205 ± 60	98 ± 42	109 ± 41	15 ± 13	18 ± 12	25 (11)	4 (8)	31 (14)	8 (16)	28 (13)	9 (18)
Di Mauro	NA	NA	NA	NA	30	33	NA	NA	9 (13)	15 (8)	3 (4)	14 (7)
Kaneko	193 ± 60*	201 ± 65*	127 ± 58*	132 ± 65*	21 ± 10*	22 ± 10*	13 (5)	2 (3)	12 (4)	5 (6)	3 (1)	0 (0)
Okada	NA	NA	NA	NA	NA	NA	NA	NA	10 (11)	23 (9)	NA	NA
Average	177 (161-193)	188 (176-200)	102 (91-114)	113 (104-123)	30 (26-34)	34 (30-39)	15.8% (12.0-20.5)	9.8% (7.3-13.1)	10.9% (8.1-14.5)	6.5% (4.5-9.4)	7.7% (4.7-12.6)	10.5% (6.7-16.2)

CPB, Cardiopulmonary bypass; TND, temporary neurologic deficit; HCA, hypothermic circulatory arrest; RCP, retrograde cerebral perfusion; NA, not available. *Mean and standard deviation calculated from median/interquartile range using techniques of Wan and colleagues.¹⁰