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Systematic Review

Antegrade *Versus* Retrograde Cerebral Perfusion in Aortic Surgery: Systematic Review and Meta-Analysis of 19365 Patients

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ABSTRACT

Background

Since the risk of neurological injury and mortality can be mitigated with the appropriate choice of established brain protection strategies, we performed a meta-analysis of studies reporting cerebral perfusion strategy outcomes. Our focus was on surgeries that can be performed through a minimally-invasive approach, to support the decision-making process of adopting surgeons.

Methods

We searched the Excerpta Medica dataBASE (EMBASE), Medical literature analysis and retrieval system online (MEDLINE), and Cochrane databases, as well as ClinicalTrials.gov, Google Scholar, and the reference lists of relevant articles for studies reporting early mortality and/or stroke outcomes of both retrograde cerebral perfusion (RCP) and antegrade cerebral perfusion (ACP) strategies. The principal summary measures were odds ratio (OR) with 95% confidence interval (CI) and *p* values (statistically significant when <0.05). The pooled ORs were combined across studies that met the eligibility criteria.

Results

We identified and included seventeen eligible studies with a total of 19,365 patients undergoing ascending aorta and arch surgery from 2008-2019 by means of ACP (a total of 10,473 patients) or RCP (a total of 8,892 patients). Random effect model analyses found no increase in mortality (OR=1.03, 95%CI:0.80-1.32) or stroke (OR=1.04, 95%CI:0.81-1.32) associated RCP when compared to ACP (p>0.05).

Conclusion

In ascending aorta and arch surgery, requiring cerebral protection, ACP and RCP have similar rates of early mortality and stroke. While optimal application of cerebral protection strategies is both patient and surgeon specific, surgeons can comfortably adopt RCP in minimally invasive cases after accounting for factors that determine the outcomes of aortic surgery adequately.

Keywords

Antegrade; Retrograde; Cerebral protection; Aorta and great vessels; Minimally invasive cardiac surgery.

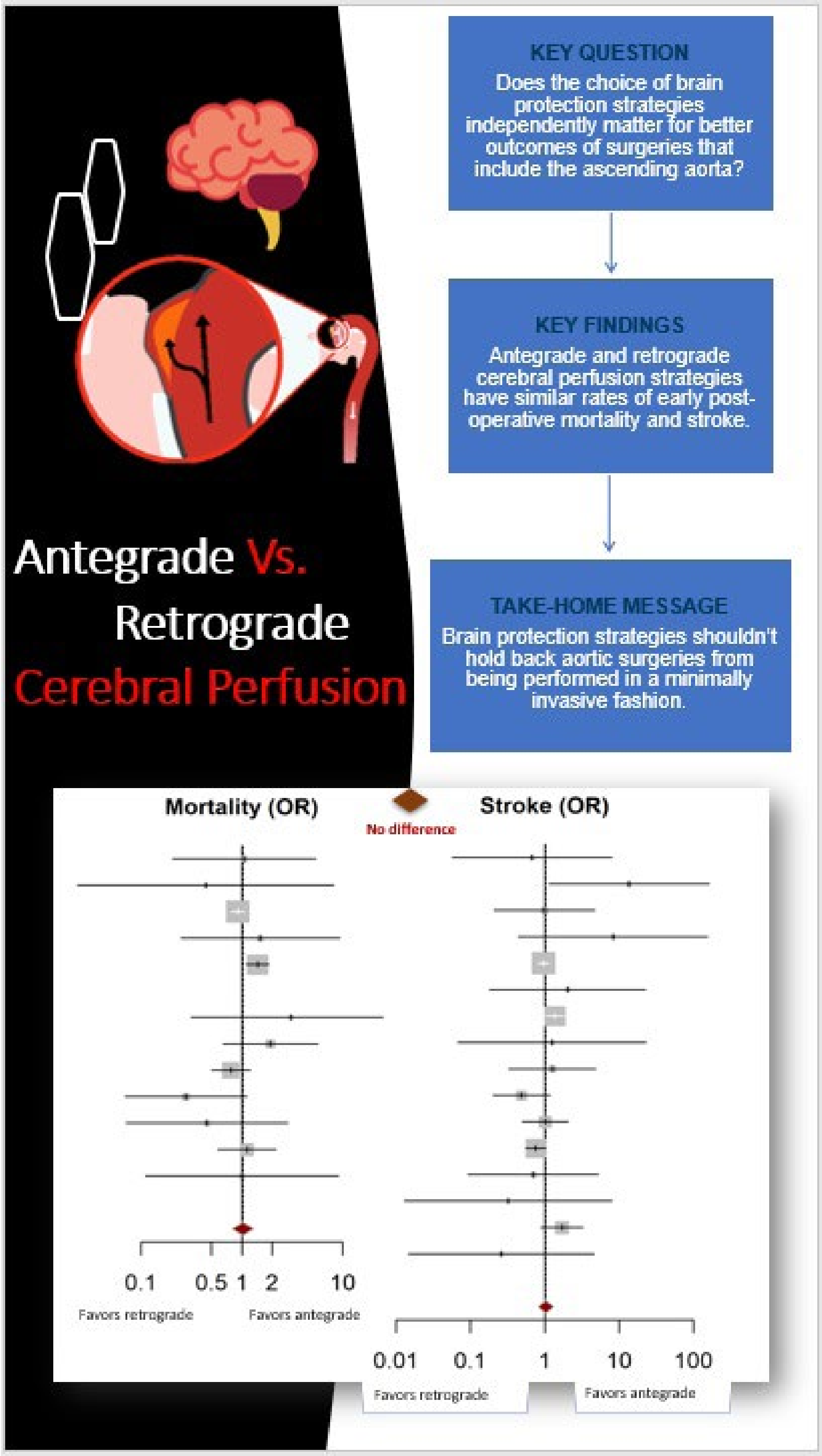
VIRTUAL ABSTRACT

Antegrade *vs* retrograde cerebral perfusion (Figure 1).

CENTRAL PICTURE

Feasibility of retrograde cerebral perfusion (RCP) through a minithoracotomy incision (Figure 2).

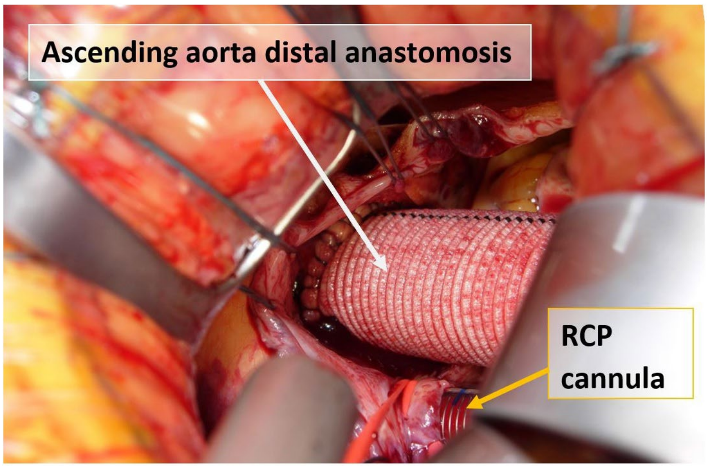
Figure 1. *Virtual Abstract*



CENTRAL MESSAGE

Different cerebral protection strategies can affect outcomes and mitigate risk differently. However, there is no measurable difference in early mortality or stroke between Antegrade cerebral perfusion (ACP) and RCP strategies in ascending/hemiarch patients. Thus, the limited choice of cerebral protection in minimally invasive approaches should not deter surgeons from using RCP in applicable cases.

Figure 2. *Ascending Aorta Distal Anastomosis*



INTRODUCTION

Rationale

Early mortality, as well as cerebrovascular injury, are two of the main concerns following ascending aorta and aortic arch surgery.[1] It has been long debated whether method of brain protection strategy can play a role in mitigating the risk of morbidity and mortality. Aortic surgery has many technical variations affecting the outcomes, not only ACP *vs* RCP, and these variables are hard to control. However, it is still unclear whether perfusion strategies, per se, can be adequate to determine the outcome of aortic surgery.

While the key to success is the combination of optimal steps based upon clinical circumstances, our meta-analysis attempts to determine if there is any measurable difference between ACP and RCP strategies to help surgeons in their decision-making process and support those adopting minimally invasive approaches.

Objectives

We performed a systematic review with meta-analysis in order to strictly compare ACP *vs* RCP during ascending aorta and aortic arch surgery, by means of an internationally recognized protocol for meta-analyses of observational studies in epidemiology [the meta-analyses of observational studies in epidemiology [MOOSE protocol].[2]

METHODS

Eligibility Criteria

Using the population, intervention, comparison, outcomes and study (PICOS) design strategy, we used the following inclusion and exclusion criteria:

Inclusion Criteria:

1. The population comprised patients undergoing ascending aorta and/or arch surgery; AND
2. There was an intervention group undergoing retrograde perfusion; AND
3. There was a control group undergoing antegrade perfusion; AND
4. Outcomes included any of the following: 30-day or operative mortality, stroke, cardiopulmonary bypass (CPB) time, aortic cross-clamp (XC) time and circulatory arrest (CA) time.

Exclusion Criteria

1. Studies were completely performed in the acute setting; OR
2. Insufficient data regarding the extent of the aneurysm; OR
3. Full length text was not accessible.

Information Sources

The following databases were searched for articles meeting our inclusion criteria and published through March 2020: PubMed/Medical literature analysis and retrieval system online (MEDLINE), Excerpta Medica dataBASE (EMBASE), cochrane controlled trials register (CENTRAL/CCTR); ClinicalTrials.gov and Google Scholar.

Search

An English language literature search was carried out by two medical librarians for medical subject heading terms and keywords that included combinations of "ascending aorta," "aortic arch surgery," "RCP" and "ACP". The related articles and additional references in identified articles were used to expand the search.

Study Selection

The following steps were taken: 1) identification of titles of relevant articles through database searches, 2) removal of duplicates, 3) screening and selection of abstracts, 4) assessment for eligibility of full-text articles, 5) hard search for relevant studies from the citing articles and 6) final inclusion in study.

Data Items

The primary endpoints were operative mortality (within 30-days or during the same admission) and stroke. Time-related endpoints considered for further analysis were CPB, XC, and CA times. For continuous data regarding time-related endpoints obtained from studies reporting the median and the interquartile ranges, a mean and a standard deviation was estimated according to Hozo's method depending on the sample size and variables distribution of each study.[3]

Data Collection Process

Two independent reviewers extracted the data. When concordance was absent, a third reviewer checked the data and made the final decision. From each study, we extracted patient characteristics, study design, and outcomes. In cases of studies with multivariable adjustment for possible confounders, outcome values from the propensity matched cases were utilized. Bilateral ACP outcomes were obtained. Studies comparing unilateral to bilateral ACP were excluded, since bilateral perfusion may be more advantageous when considering existing atherosclerotic conditions.

Summary Measures

Odds ratio (OR) with 95% confidence interval (CI) and p-values (considered statistically significant when $p<0.05$) for the crude endpoints were calculated. For other comparative data, differences in means with 95% CI and p-values (considered statistically significant when $p<0.05$) were considered. All analyses were completed with R statistical software (version 4.0.2). All statistical tests were two-sided, with statistical significance set at $p<0.05$.

Synthesis of Results

Forest plots represent the clinical outcomes. Chi-square (χ^2) test and I2 test were performed for assessment of statistical heterogeneity.[4] The OR and differences in means were combined across the studies using random-effects models.

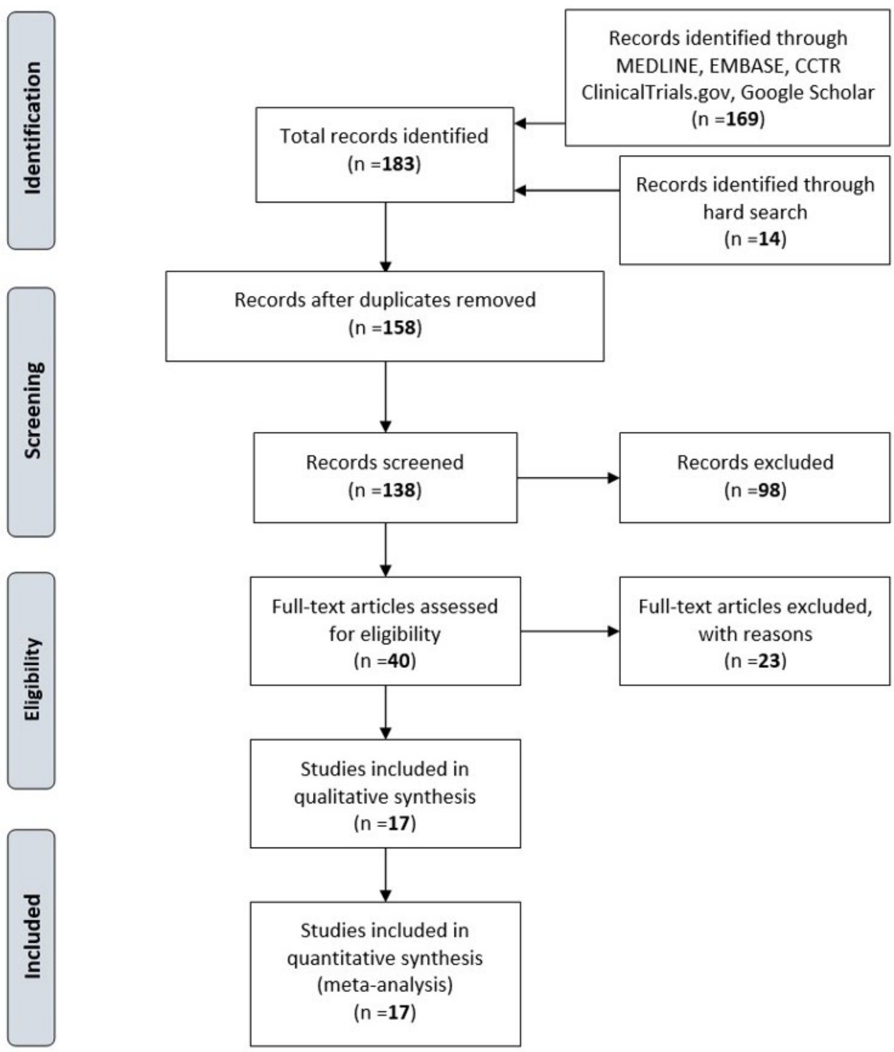
Funnel plots represent the analysis of publication bias, statistically analyzed by Begg and Mazumdar's test[5] and Egger's test.[6]

RESULTS

Study Selection

A total of 183 citations were identified, of which 40 studies were

Figure 3. *Flow Diagram of Studies Included in Data Search. Embase, Medline, Cochrane Controlled Trials Register (CCTR), ClinicalTrials.gov, and Google Scholar*



potentially relevant and retrieved as full text. Seventeen (17) publications[7-23] fulfilled our eligibility criteria (Figure 3).

Study Characteristics

A total of 19,365 patients (RCP: 8,892 patients; ACP: 10,473 patients) were included from studies published from 2008 to 2019. Most of the studies (n=10, 59%) were non-randomized and retrospective, five studies (24%) were propensity-matched and two were randomized controlled trials (Table 1).

Synthesis of Results

Primary outcomes: Early mortality was defined as all-cause mortality within 30-days and/or during hospitalization. The OR for early mortality in the ACP group compared with the RCP group in each study is reported in Figure 4 (A). All-cause mortality within 30-days were observed in thirteen studies comprising a total of 1274 events among 17926 patients. There was evidence of low-moderate heterogeneity of treatment effect among the studies for early mortality. The overall OR (95% CI) of early mortality showed no statistically significant difference between ACP and RCP, confirming no risk increase in the RCP group (random effects model: 1.03, 95% CI: 0.80-1.32, p=0.815).

Stroke was defined as the presence of a permanent neurologic deficit persisting at time of discharge, confirmed with imaging modality when possible. The OR for stroke in the ACP group compared with the RCP group in each study is reported in Figure 4 (B). Post-operative permanent strokes were observed in sixteen trials comprising a total of 1133 events among 18669 patients. There was evidence of low-moderate heterogeneity of treatment effect among the studies for stroke. The overall OR (95% CI) of stroke showed no statistically significant difference between ACP and RCP, confirming no risk increase of permanent stroke for RCP (random effects model: 1.04, 95% CI: 0.81-1.32, p=0.759).

Other endpoints results: Procedure-related times and their relationship with the extent of the aortic replacement were summarized in Table 2. Hypothermic CA times were reported in eleven studies comprised of 7784 patients, XC times were reported in nine studies comprised of 4036 patients, while pump times (CPB) were reported in ten studies comprised of 4729 patients.

The difference in means for CA time (minutes) in the ACP group compared with the RCP group in each study is reported in Figure 5 (A). There was evidence of high heterogeneity of treatment effect among the studies for CA time. The overall difference in means (95% CI) for CA time showed no statistically significant difference between ACP and RCP (random effects model: -0.91, 95% CI: -6.45-4.62, p=0.720).

The difference in means for XC time (minutes) in the ACP group compared with the RCP group in each study is reported in Figure 5 (B). There was evidence of high heterogeneity of treatment effect among the studies for XC time. The overall

Table 1. *Patient Baseline Characteristics in Comparative Studies Comparing Antegrade vs Retrograde Cerebral Perfusion*

Authors	Country	Type	Total (n) +	Age		Sex (Female)		Etiology**		Non-Elective Cases**	
				ACP	RCP	ACP (%)	RCP (%)	Dissection	Aneurysm	ACP (%)	RCP (%)
Abdelgawad et al[7]	Egypt	R	43	60.19±15.48	58.52±15.56	2 (11.1)	3 (12.0)	√	√	6 (33.3)	7 (28)
Apaydin et al[8]	Turkey	R	113	60±13	54±12	48 (30)	0	√	√		
Arnaoutakis et al[9]	USA	R	589	61.9±13.4	60.4±13.0	29 (25.4)	145 (31.2)		√	0%	
Di Mauro et al[10]	Saudi Arabia	R	208	63±12		150 (33)		√	√		
Englum et al[11]	USA	R	7567	62 (IQR 52.0-72)		4,263 (34)		√	√	64%	
Ganapathi et al[12]	USA	M	160	50.7±14.2	50.9±13.7	30 (37.5)	34 (42.5)	√	√	11 (13.8)	9 (11.3)
Itagaki et al[13]	USA	R	5257	62.7±13.0	62.7±13.7	1182 (35.1)	635 (33.5)		√	182 (5.4)	87 (4.6)
Leshnower et al[14]	USA	RCT	20	58±12	56±14	2 (22)	0 (0)		√	0%	
Milewski et al[15]	Italy/USA	M	776	64.1±11.5	59.9±15.3	34 (36)	215 (32)		√	0%	
Misfeld et al[16]	Germany	R	293	62±14	62±14	90 (37)	13 (25)	√	√	90 (37)	12 (24)
Okada et al[17]	Japan	R	405	63±13		150 (30)		√	√	21%	
Okita et al[18]	Japan	M	2282	70.5±10.1	68.3±11.6	340 (29)	321 (28)		√	0%	
Perreas et al[19]	Greece	M	80	61.3±11.4	62.8±13.1	12 (23)	14 (35)	√	√	24 (60)	29 (73)
Sundt et al[20]	USA	R	77	64±16	71±8	36 (49)	27 (51)	√	√	0%*	
Svensson et al[21]	USA	RCT	121	58±13	58±12	21 (34)	27 (45)	√	√		
Usui et al[22]	Japan	M	998	67.8±12.2	67.5±11.3	166 (33)	165 (33)		√		
Vallabhajosyula et al[23]	USA	R	376	66±11	60±14	26 (35)	107 (36)		√	43%	

*ACP: antegrade cerebral perfusion; M: propensity-matched study; R: retrospective study; RCP: retrograde cerebral perfusion; RCT: randomized-controlled trial. +Total number of cases used for the analysis; *In our analysis only outcomes data from elective cases were used.*
***Unfortunately, some important information about proportions of etiology type and the emergency nature of procedure were only presented by part of the studies and could not be compared.*

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Figure 4. *Forest plots. Pooled odds ratio and conclusions plot for: (A) Early mortality, and (B) Stroke. CI, confidence interval*

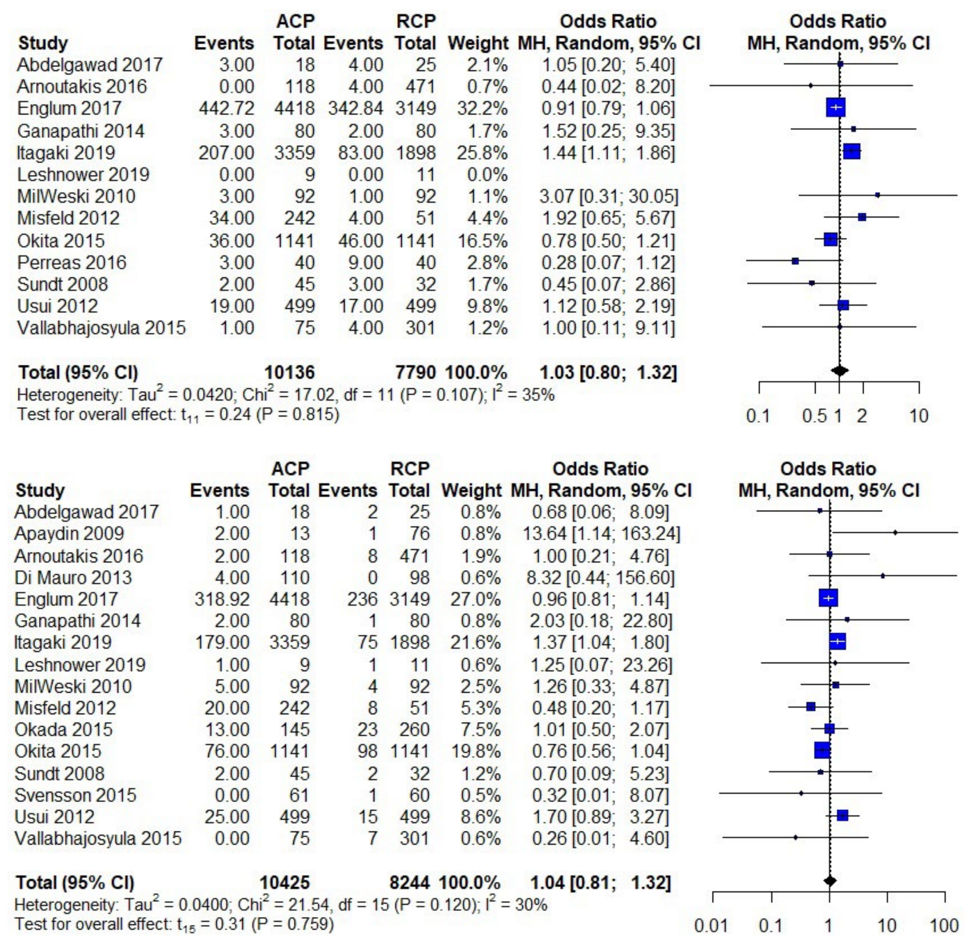
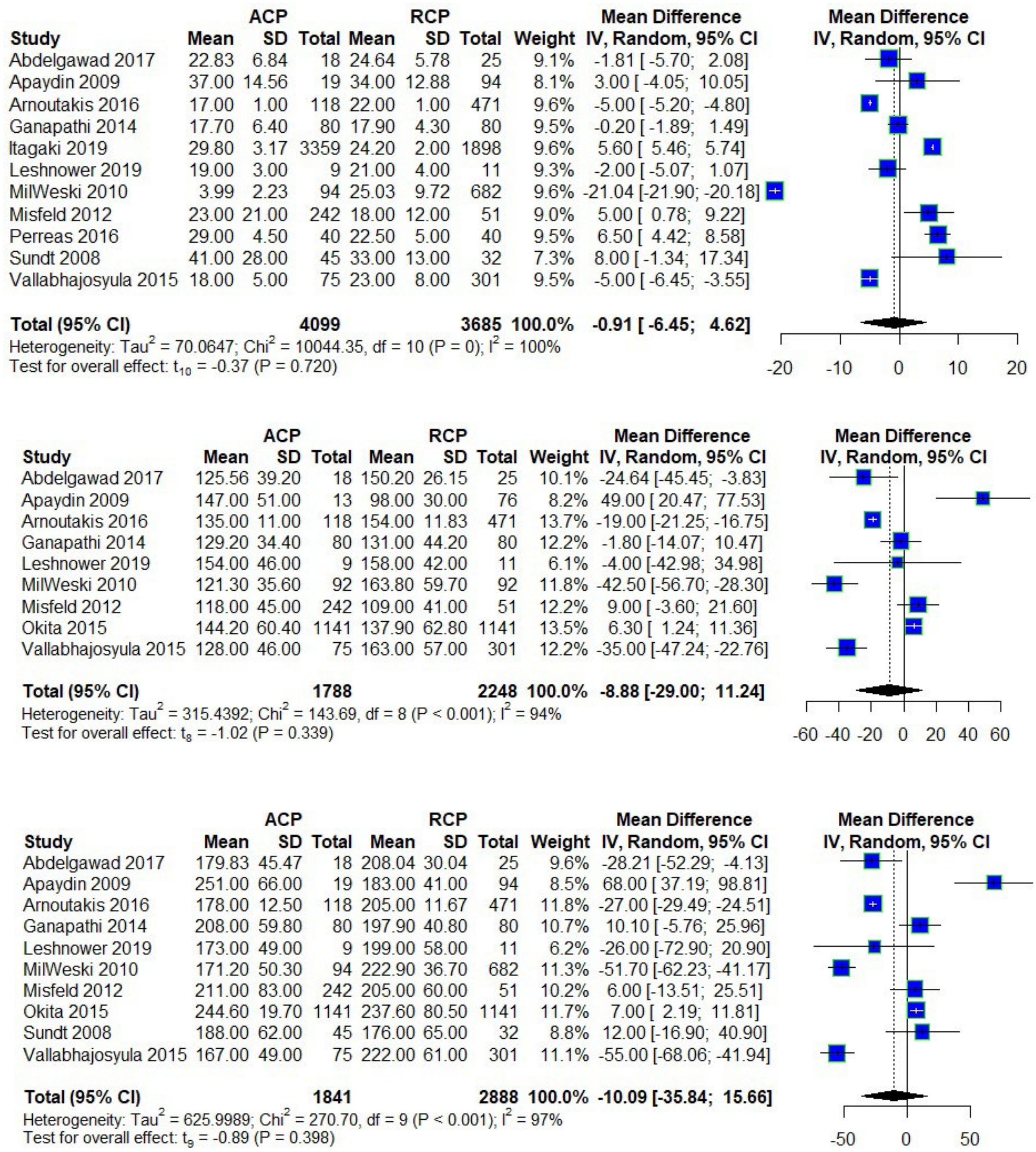


Table 2. *Characteristics of Relevant Articles Identified for Meta-Analysis Comparing Antegrade vs Retrograde Cerebral Perfusion*

Authors	Total		Intervention			CA Time		XC Time		CPB Time	
	ACP	RCP	Ascending Aorta Only	Total Arch	Hemiarch	ACP	RCP	ACP	RCP	ACP	RCP
Abdelgawad et al[7]	18	25	√		√	22.83±6.84	24.64±5.78	125.56±39.20	150.20±26.15	179.83±45.47	208.04±30.04
Apaydin et al[8]	19	94	√	√		28±12	40±11	147±51	98±30	251±66	183±41
Arnaoutakis et al[9]	118	471			√	17 (IQR 14-20)	22 (IQR 19-25)	135 (98-164)	154 (IQR 121-192)	178 (IQR 140-215)	205 (IQR 175-245)
Englum et al[11]*	4418	3149	√	√	√	27 (IQR 19-41)		NR		185 (IQR 149-235)	
Ganapathi et al[12]	80	80			√	17.7±6.4	17.9±4.3	129.2±34.4	131.0±44.2	208±59.8	197.9±40.8
Itagaki et al[13]	3359	1898		√	√	29.8 (IQR 18-37)	24.2 (IQR 16-28)	NR		NR	
Leshnower et al[14]	9	11		√	√	3.99±2.23	25.03±9.719	121.3±35.6	163.8±59.7	171.2±50.3	229.9±63.7
Milewski et al[15]	94	682		√	√	3.99±2.23	25.03±9.719	121.3±35.6	163.8±59.7	171.2±50.3	229.9±63.7
Misfeld et al[16]	242	51		√	√	23±21	18±12	118±45	109±41	211±83	205±60
Okita et al[18]	1141	1141		√		NR		144.2±60.4	137.9±62.8	244.6±91.7	237.6±80.5
Perreas et al[19]	40	40	√		√	29 (IQR 24-42)	22.5 (IQR 17-37)	NR		NR	
Sundt et al[20]	45	32	√	√	√	41±28	33±3	NR		188±62	176±65
Svensson et al[21]*	61	60		√		27±13		NR		118±33	
Vallabhajosyula et al[23]	75	301			√	18±5	23±8	128±46	163±57	167±49	222±61

ACP: antegrade cerebral perfusion; CA: circulatory arrest; CPB: cardiopulmonary bypass; NR: not reported RCP: retrograde cerebral perfusion; XC: cross-clamp.
**In our pooled continuous data meta-analysis these studies were excluded.*

Figure 5. *Forest Plots. Pooled Adds Ratio and Conclusions Plot for: (A) Circulatory Arrest Time, (B) Cross-clamp time, and (C) Cardiopulmonary Bypass Time. CI, Confidence Interval*



difference in means (95% CI) for XC time showed no statistically significant difference between ACP and RCP (random effects model: -8.88, 95% CI: -29.00-11.24, p=0.339).

The difference in means for CPB time (minutes) in the ACP group compared with the RCP group in each study is reported in Figure 5 (C). There was evidence of high heterogeneity of treatment effect among the studies for CPB time. The overall difference in means (95% CI) for CPB time showed no statistically significant difference between ACP and RCP (random effects model: -10.09, 95% CI: -35.84-15.66, p=0.398).

Risk of Bias Across Studies

Funnel plot analysis (Figure 6) did not disclose any asymmetry around the axis for the treatment effect in any of the studied outcomes. Consequently, publication bias related to the outcomes is unlikely.

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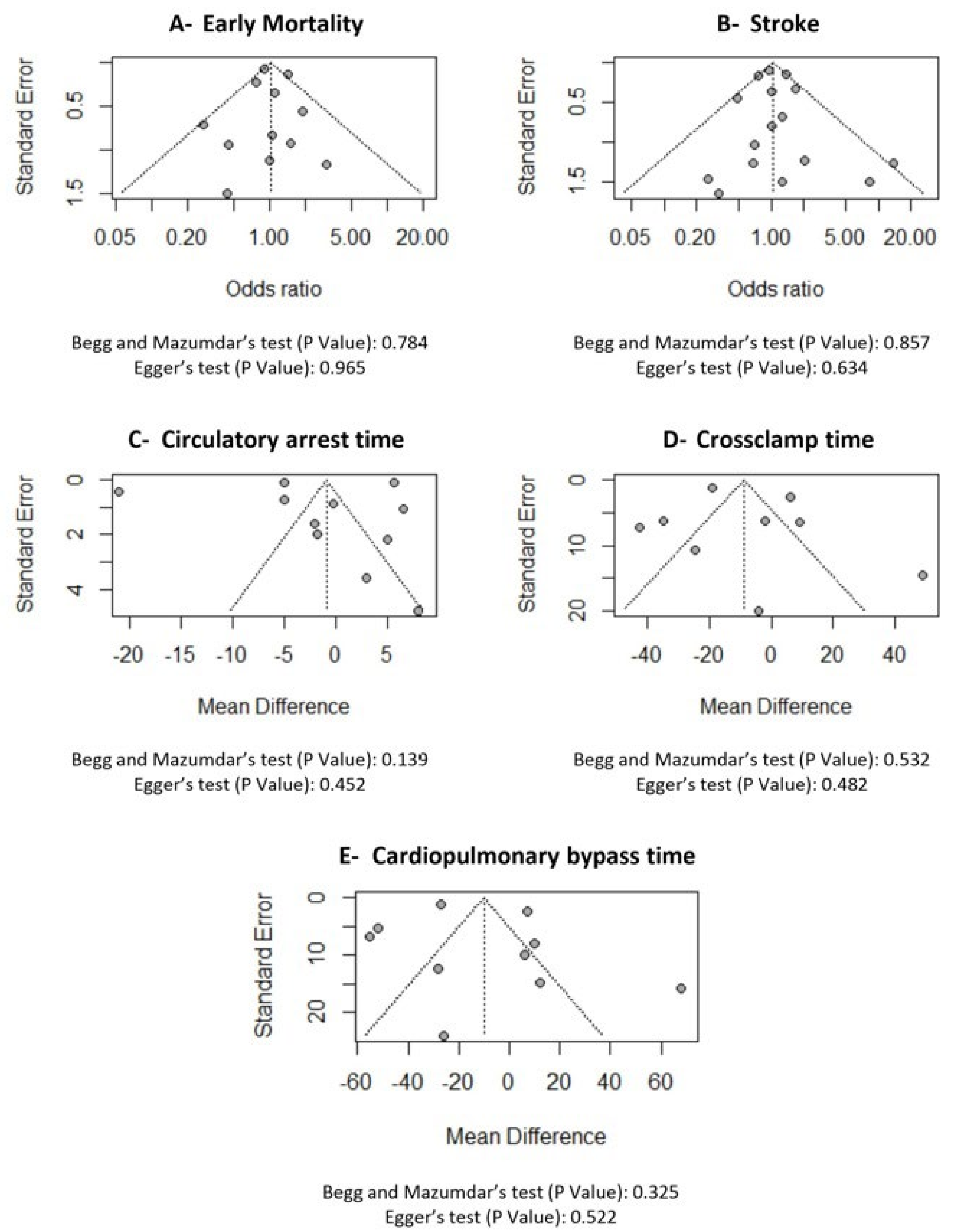
Figure 6. *Publication Bias. Funnel Plots for: (A) Early Mortality, (B) Stroke, (C) Circulatory Arrest Time, (D) Cross-Clamp Time, and (E) Cardiopulmonary Bypass Time*



DISCUSSION

Summary of Evidence

The results of this meta-analysis demonstrated no statistically significant difference favoring one cerebral perfusion strategy over the other in terms of early mortality and neurological deficits. The combined studies and their groups were balanced in terms of age and sex. Both strategies did not result in significantly different cross-clamp, cerebral perfusion, or bypass times (p>0.05). The pooled ORs for early operative mortality and stroke revealed no statistically significant difference between the groups (p>0.05), which indicates that patients undergoing ACP during aortic surgery had no advantage over RCP. The summary measures were under low influence of heterogeneity of the effects or publication bias.

To date, no large, multicenter, high-quality, randomized controlled trial has compared RCP *vs* ACP in terms of effectiveness and outcomes, which may not be necessary, however, while our ability to put forward any robust evidence-based recommendations regarding perfusion strategies, it is highlighting the importance of data-driven evidence in scenarios where surgeons are not putting their best foot forward to adopt minimally invasive approaches for aortic pathologies.

Considerations about this Meta-Analysis

An ongoing debate between ACP *vs* RCP has remained unsettled over the past three decades. ACP requires a more complex cannulation and perfusion setup, but it ensures direct cerebral perfusion. However, the notion that ACP provides superior protection and adds a "safety net," has not been scientifically proven and remains a matter of discussion. Since ACP has not been proven to be superior to RCP,[24-27] it is certainly important to continue studying this issue, especially in centers implementing evolving lesser invasive techniques (such as minimally invasive methods, or purely endovascular and "hybrid" endovascular and surgical approaches).[28-31]

We have shown that RCP in the setting of a right minithoracotomy approach is feasible and safe.[28] Furthermore, it is the only choice for cerebral protection in such setting when considering a hemi-arch surgery.[1] RCP is also performed without manipulation of the aortic arch vessels, *via* superior vena cava cannulation, allowing sustained cerebral perfusion during hypothermic CA and retrograde removal of embolic material from the arterial circulation of the brain.[32] It increases the effectiveness of brain protection from healthcare assistant (HCA) alone, from less than 30-minutes to about 40-60-minutes.[33] Experimental studies may have been misinterpreted in terms of inferiority of RCP when compared to ACP in animal models.[34] However, despite several extreme CA times and varying degrees of body temperature, RCP maintained a neurologic protective benefit.[35-39] The main limitation of animal studies is the different anatomy of the jugular venous system compared to humans. Despite this, the inferiority of RCP to ACP as a cerebral protection strategy was debunked in previous studies and confirmed in ours as well.[24-27]

What is Different from Previous Large Meta-Analyses?

The ascending aorta and arch were the main anatomical focus of the intervention in our study. Previous meta-analyses did not consider the status of the patient cohort.[24-27] We excluded studies performed completely in an emergent setting, aiming to reduce the confounding effect of evolving neurological dysfunction in patients presenting with acute Type A dissections. Furthermore, our study stands out from previously published meta-analyses by including published studies over the last decade, reducing historical bias, yet still having a pooled sample size that is threefold larger than the frequently cited studies of Hu et al[24] and Guo et al.[25]

All these characteristics will help readers develop a more in-depth and detailed view for better critical analysis of the recently published literature on aortic surgery.

Risk of Bias and Limitations

This study shares the inherent limitations of meta-analyses, such as including non-randomized and/or observational studies. Although our study reflects real-world data, they may be limited by treatment bias, the presence of unmeasured confounders, and a tendency to overestimate treatment effects. Heterogeneity may still exist, especially in sample size and surgical expertise. Center volume may have led to this influence of clinical heterogeneity not captured by the meta-analysis. In contrast, individual patient data could have enabled us to conduct further subgroup analysis to account for differences between the treatment groups.

Future Perspectives

Our findings support the benefit of both cerebral protection strategies in terms of neuroprotection and survival during circulatory arrest. However, RCP cannulation is less complicated than ACP and does not require exposure or manipulation of the arch vessels. In addition, there was no significant additional surgical time incurred when compared with ACP. RCP can be performed as the standard neuroprotection strategy in less-experienced centers as well as in sophisticated, minimally invasive approaches without increase in CA, XC and CPB times.

CONCLUSION

RCP in patients undergoing ascending aortic and aortic arch surgery provides equivalent outcomes to those of ACP. The results of this study suggest the need for a personalized approach to patient-specific scenarios, while considering surgeons preference, to mitigate the inherent risky nature of ascending aortic and aortic arch surgery.

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DISCLOSURE

None.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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