Featured Article

Comparison between antegrade and retrograde cerebral perfusion or profound hypothermia as brain protection strategies during repair of type A aortic dissection

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Background: The goal of this study was to compare early postoperative outcomes and actuarial-free survival between patients who underwent repair of acute type A aortic dissection by the method of cerebral perfusion used.

Methods: A total of 324 patients from five academic medical centers underwent repair of acute type A aortic dissection between January 2000 and December 2010. Of those, antegrade cerebral perfusion (ACP) was used for 84 patients, retrograde cerebral perfusion (RCP) was used for 55 patients, and deep hypothermic circulatory arrest (DHCA) was used for 184 patients during repair. Major morbidity, operative mortality, and 5-year actuarial survival were compared between groups. Multivariate logistic regression was used to determine predictors of operative mortality and Cox Regression hazard ratios were calculated to determine the predictors of long term mortality.

Results: Operative mortality was not influenced by the type of cerebral protection (19% for ACP, 14.5% for RCP and 19.1% for DHCA, P=0.729). In multivariable logistic regression analysis, hemodynamic instability [odds ratio (OR) =19.6, 95% confidence intervals (CI), 0.102–0.414, P<0.001] and CPB time >200 min (OR =4.7, 95% CI, 1.962–1.072, P=0.029) emerged as independent predictors of operative mortality. Actuarial 5-year survival was unchanged by cerebral protection modality (48.8% for ACP, 61.8% for RCP and 66.8% for no cerebral protection, log-rank P=0.844).

Conclusions: During surgical repair of type A aortic dissection, ACP, RCP or DHCA are safe strategies for cerebral protection in selected patients with type A aortic dissection.

Keywords: Aorta; aortic dissection; cerebral protection

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Introduction

Surgical repair of acute type A aortic dissections is associated with high mortality, which ranges from 2.8% to 30%. This is often attributed to the emergent nature of the procedure, an elderly patient population, severe comorbidities, and oftentimes a large extent of aorta needing replacement (1-9). The necessity to clamp many of the large arteries supplying the brain during repair has consequently led to a heightened risk of permanent neurological damage (1). Damage to the brain is the most prevalent complication following aortic surgery (1-12). Attempts to mitigate this risk have evolved over time from the use of deep hypothermic circulatory arrest (DHCA) alone, to DHCA with retrograde cerebral perfusion (RCP), and finally to moderate hypothermic circulatory arrest (MHCA) with unilateral or bilateral antegrade cerebral perfusion (ACP) (1,13).

We sought to evaluate the efficacy of cerebral protection strategies for patients following repair of acute type A aortic dissection. We compared the early and late outcomes between ACP, RCP and DHCA as neuroprotective strategies during repair of type A aortic dissection.

Methods

Patients

The Society of Thoracic Surgeons Databases at Beth Israel Deaconess, Carolinas Medical Center, Missouri Baptist Medical Center, Meijer Heart and Vascular Institute, and the University of Iowa Hospitals and Clinics were queried to identify all patients who underwent repair of aortic dissection between January 2000 and December 2010 and utilized either ACP, RCP or DHCA during surgery. A total of 324 patients underwent repair for acute type A aortic dissection. Of those, 84 were repaired using ACP, 55 had RCP and 184 had DHCA. Patients excluded were those that presented with a type A dissection who did not have surgery.

A preoperative diagnosis of aortic dissection was accomplished using computed tomography angiography (CTA) or transesophageal echocardiography (TEE). The diagnosis was later confirmed at the time of operation. A database was created for entry of demographic, procedural data and postoperative outcomes. These were prospectively entered by dedicated data-coordinating personnel. Long-term survival data were obtained from the Social Security Death Index (http://search.ancestry.com/search/db.aspx?dbid=3693).

Prior to this analysis, study approval from the Institutional Review Boards of each center was obtained. Consistent with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), patient confidentiality was consistently maintained.

Definitions

The Society of Thoracic Surgeons' national cardiac surgery database definitions were used for this study. Acute type A dissection was defined as any dissection that involved the ascending aorta with presentation within two weeks of the onset of symptoms. Previous cerebrovascular accident was defined as history of central neurologic deficit persisting for more than 24 h. Chronic renal insufficiency was defined as a serum creatinine value >2.0 mg/dL. Diabetes was defined as a history of diabetes mellitus, regardless of duration of disease or need for oral agents or insulin. Recent myocardial infarction was defined as myocardial infarction occurring within 7 days. Depressed ejection fraction was defined as ejection fraction <40%. Hemodynamic instability was defined as hypotension (systolic blood pressure <80 mmHg) or the presence of cardiac tamponade, shock, acute congestive heart failure, myocardial ischemia and or infarction. Prolonged ventilatory support was defined as pulmonary insufficiency requiring ventilatory support >24 hours, postoperatively. Postoperative stroke was defined as any new major (type I) neurologic deficit presenting in-hospital and persisting >72 hours. Acute renal failure was defined as one or both of the following: (I) an increase in the serum creatinine to >2.0 mg/dL and/or a >2-fold increase in the most recent preoperative creatinine level or (II) a new requirement for dialysis, postoperatively. Operative mortality included both (I) all deaths occurring during the hospitalization in which the operation was performed (even if death occurred after 30 days from the operation); and (II) those deaths occurring after discharge from the hospital, but within 30 days of the procedure.

Operative technique

The surgical approach was consistent irrespective of the type of cerebral protection used. The choice of cerebral protection strategy varied between surgeons but there were no significant differences in the strategy between hospitals. Intraoperatively, the diagnosis of type A aortic dissection was confirmed by TEE for all patients. A median sternotomy was created to provide access. Total cardiopulmonary bypass (CPB) was provided by arterial cannulation of the femoral or right axillary artery and venous cannulation of the right atrium. Cold blood cardioplegia administration through an antegrade approach via the ostia of the coronary arteries and/or a retrograde approach through the coronary sinus was performed to ensure myocardial protection. If cerebral protection was indicated, it was initiated at this time through the use of either an antegrade or retrograde approach. ACP was initiated through the right axillary artery, while RCP was initiated through the superior vena cava. The right superior pulmonary vein provided access for vent placement in the left ventricle. Restoration of the aortic root was accomplished by resection of the intimal tear followed by repair or resuspension of the aortic valve and replacement of the ascending aorta. After reaching a mean cooling temperature range of 10 to 24 ℃ for DHCA or 25 to 32 ℃ for MHCA, the aortic clamp was removed and the aortic arch was examined. An arch replacement was performed when an arch tear was identified. The distal anastomosis was then completed and antegrade aortic perfusion was established. If the aortic valve and the sinuses were normal, resuspension of the aortic valve was performed by placing three polypropelene pledgeted sutures at the three valve commissures, along with replacement of the ascending aorta with a straight tube graft. If the aortic valve was structurally abnormal, but the sinuses were normal, aortic valve replacement with mechanical or tissue prosthesis and supracoronary aortic grafting were performed. If the aortic valve and sinuses were abnormal, from dilation (more than 5 cm), or extension of the intimal tear to the valve, aortic root replacement (modified Bentall operation) with a tissue or mechanical valved-conduit was used. Teflon (polytetrafluoroethylene) strips were used to reinforce the proximal and distal anastomosis. In some patients, biological glue (BioGlue® surgical adhesive, Cryolife, Kennesaw, GA, USA) was used to better reapproximate the dissected layers.

Data analysis

Univariate analysis

Univariate comparisons of preoperative, operative, and postoperative variables were performed between patients repaired utilizing DHCA (n=184), ACP (n=84), and RCP (n=55). Normal distribution of continuous variables was assessed using the Kolmogorov-Smirnov test. Continuous variables were tested using either the one-way ANOVA test, while categorical variables were assessed by the chi-square or Fisher exact test, depending on the distribution of data. All tests were two-sided and a P value of <0.05 was considered statistically significant.

Multivariable analysis

A multivariable, stepwise, forward logistic regression analysis was conducted to determine independent predictors of operative mortality. The criterion for variable entry into the logistic model was a univariate probability level of P<0.100. The quality of the fit of the logistic model was tested with the Hosmer–Lemeshow goodness-of-fit test.

Survival analysis

Kaplan-Meier univariate unadjusted survival estimates were calculated and compared using a log-rank test for patients repaired utilizing ACP, RCP or DHCA. Cox Regression hazard ratios were calculated to determine the predictors of long term mortality. All analyses were conducted using SPSS statistical software Version 21 (IBM Corp, Armonk, NY, USA).

Results

Preoperative characteristics

Preoperative characteristics are summarized in *Table 1*. Only ejection fraction varied between the three groups (P=0.033). The Games Howell post-hoc test showed a higher ejection fraction in the RCP group compared to DHCA patients.

Operative characteristics

Operative characteristics of patients repaired utilizing ACP, RCP or DHCA, who underwent repair for acute type A aortic dissection are presented in *Table 2*. Patients repaired using ACP more frequently had prolonged CPB times (longer than 200 minutes), compared to patients who underwent DHCA or RCP (P=0.003). ACP patients had a longer average CPB time (P=0.023), in comparison with patients who underwent DHCA or RCP, as shown by the Bonferroni post-hoc test. Patients repaired using RCP had a longer average circulatory arrest time than those repaired with ACP or DHCA (P<0.001), with ACP having a longer average time compared to patients repaired under DHCA. A total arch replacement was required more frequently for patients repaired using ACP compared to patients repaired with DHCA or RCP (P<0.001). Circulatory arrest temperatures were lower in DHCA patients, while ACP patients had higher circulatory arrest temperatures (P=0.040). RCP was performed at a lower temperature than ACP.

Postoperative characteristics

Postoperative characteristics are depicted in *Table 3*. There was no difference in postoperative outcomes between patients who underwent ACP, RCP or DHCA during surgical repair.

Table 1 Preoperative patient characteristics

Variable[a]	DHCA (n=184)	ACP (n=84)	RCP (n=55)	P value
Age (years)	59 [19–83]	58 [29–87]	62 [23–83]	0.314
Diabetes	15 (8.2%)	6 (7.1%)	3 (5.5%)	0.794
Hypertension	137 (74.5%)	67 (79.8%)	42 (76.4%)	0.639
Ejection fraction	56 [20–75]	58 [30–75]	59 [50–75]	0.033
COPD	14 (7.6%)	7 (8.3%)	4 (7.3%)	0.570
Creatinine	1.3 [0.6–3.8]	1.2 [0.5–3.9]	1.1 [0.4–2.4]	0.313
Female gender	59 (32.1%)	24 (28.6%)	17 (30.9%)	0.848
Arrhythmias	20 (10.9%)	7 (8.3%)	6 (10.9%)	0.803
NYHA class				0.074
I	17 (9.2%)	5 (6.0%)	4 (7.3%)	–
II	43 (23.4%)	29 (34.5%)	22 (40.0%	–
III	39 (21.2%)	16 (19.0%)	15 (27.3%)	–
IV	85 (46.2%)	34 (40.5%)	14 (25.5%)	–
Cerebrovascular accident	18 (9.8%)	4 (4.8%)	5 (9.1%)	0.378
Hemodynamic instability	27 (14.7%)	12 (14.3%)	8 (14.5%)	0.997
EF <40	10 (5.4%)	4 (4.8%)	0	0.216

[a], continuous data are shown as median (range) and categorical data are shown as percentage. ACP, antegrade cerebral perfusion; RCP, retrograde cerebral perfusion; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; NYHA, New York Heart Association.

Table 2 Operative patient characteristics

Variable[a]	DHCA (n=184)	ACP (n=84)	RCP (n=55)	P value
CPB time >200 minutes	65 (35.5%)	47 (56.0%)	28 (50.9%)	0.003
CPB time, minutes	196 [52–588]	227 [112–430]	207 [102–454]	0.023
Circulatory arrest time, minutes	17 [0–146]	31 [0–73]	36 [4–61]	<0.001
Circulatory arrest temperature, Celsius	19 [10–32]	19 [8–26]	17 [10–20]	0.040
Aortic valve procedure				0.690
Nothing	51 (27.7%)	29 (34.5%)	15 (27.3%)	–
Replacement	17 (9.2%)	5 (6.0%)	2 (3.6%)	–
Resuspension	78 (42.4%)	33 (39.3%)	27 (49.1%)	–
Bentall	38 (20.7%)	17 (20.2%)	11 (20.0%)	–
Hemiarch technique	102 (55.4%)	54 (64.3%)	37 (67.2%)	0.179
Total arch replacement	9 (4.9%)	17 (20.2%)	3 (5.5%)	<0.001

[a], continuous data are shown as median (range) and categoric data are shown as percentage. ACP, antegrade cerebral perfusion; RCP, retrograde cerebral perfusion; CPB, cardiopulmonary bypass.

Multivariate analysis

In multivariable logistic regression analysis, hemodynamic instability [odds ratio (OR), 19.6, 95% Confidence interval (CI), 0.102–0.414, P<0.001] and CPB time >200 min (OR, 4.7, 95% CI, 1.962–1.072, P=0.029) emerged as independent predictors of operative mortality.

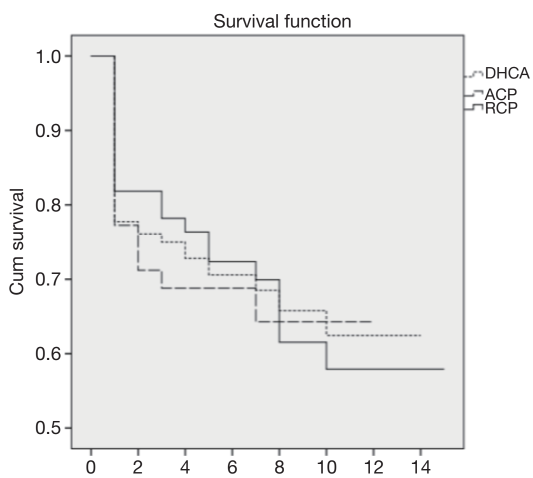
Survival analysis

Actuarial Kaplan-Meier survival estimates are presented in the *Figure 1*. There was no difference in actuarial 5-year

Table 3 Postoperative patient characteristics

Variable[a]	DHCA (n=197)	ACP (n=112)	RCP (n=55)	P value
Deep sternal wound infection	4 (2.2%)	2 (2.4%)	3 (5.5%)	0.417
Prolonged ventilation	79 (42.9%)	37 (44.0%)	27 (49.1%)	0.722
Acute renal failure	38 (20.7%)	19 (22.6%)	8 (14.4%)	0.491
Hemodialysis	18 (9.8%)	7 (8.3%)	1 (1.8%)	0.162
Hemorrhage related re-exploration	29 (15.8%)	12 (14.3%)	7 (12.7%)	0.845
Cardiac arrest	19 (10.3%)	5 (6.0%)	7 (12.7%)	0.364
Stroke	26 (14.1%)	12 (14.3%)	12 (21.8%)	0.361
Atrial fibrillation	45 (24.5%)	10 (11.9%)	12 (21.8%)	0.062
Hospital length of stay (days)	15 [0–99]	14 [1–61]	16 [5–86]	0.753
Operative mortality	35 (19.1%)	16 (19%)	8 (14.5%)	0.729

[a], continuous data are shown as median (range) and categoric data are shown as percentage. ACP, antegrade cerebral perfusion; RCP, retrograde cerebral perfusion; CPB, cardiopulmonary bypass.



Number at risk	1 year	2 year	3 year	4 year	5 year	10 year
DHCA (n=184)	143 (77.7%)	140 (76.1%)	138 (75%)	133 (72.3%)	123 (66.8%)	31 (16.8%)
ACP (n=84)	64 (76.2%)	59 (70.2%)	57 (67.9%)	52 (61.9%)	41 (48.8%)	7 (8.3%)
RCP (n=55)	45 (81.8%)	45 (81.8%)	43 (78.2%)	41 (74.5%)	34 (61.8%)	15 (27.3%)

Figure 1 Actuarial 5-year survival curves for patients repaired using ACP, RCP or DHCA during acute type A aortic dissection repair. ACP, antegrade cerebral perfusion; RCP, retrograde cerebral perfusion; DHCA, deep hypothermic circulatory arrest.

survival for patients who underwent repair with ACP, RCP or DHCA (P value =0.844). *Table 4* depicts the Cox regression hazard ratios for the predictors of late mortality.

Discussion

Our study compared early and late postoperative outcomes for patients who underwent repair of acute type A aortic dissection using ACP, RCP or DHCA. Patients who underwent surgery with ACP on average required more CPB time than those repaired with RCP or DHCA. Our results show that there is no difference in operative mortality for patients with type A aortic dissection repaired using ACP, RCP, or no cerebral protection. Hemodynamic instability and prolonged CPB times were independent predictors of operative mortality, regardless of cerebral protection strategy.

Principal findings

Operative mortality

There is a considerable debate over which cerebral perfusion method results in better brain protection and lower mortality. Our study found no difference in operative mortality with respect to ACP, RCP or DHCA during repair of acute type A aortic dissection. Other studies have also concluded that there is no difference in operative mortality between ACP and RCP (10,14-16).

While the method of cerebral perfusion may be a less important predictor of operative mortality, cerebral perfusion in general seems to be important for minimizing mortality. This seems to be less of an issue for shorter procedures where arrest times up to 30 to 40 minutes can be safely achieved with hypothermic circulatory arrest alone (2). However, Okita *et al.* reported significantly higher mortality for patients repaired with DHCA (14.5%) compared to those repaired with RCP (3.4%) (7). Similarly, Wiedemann *et al.* demonstrated higher operative mortality in patients repaired using DHCA alone (26%) compared to those who have ACP (13%) or RCP (16%) (1). Some authors have concluded

Table 4 Predictors of long term mortality

Variable	HR	95% CI	P value
Age	19.7	1.020–1.054	0.000
Hemodynamic instability	9.4	0.301–0.768	0.002
Postoperative stroke	10.5	0.302–0.745	0.001
Postoperative renal failure	9.1	0.344–0.797	0.003
Cerebral perfusion >200 min	10.8	0.351–0.768	0.001

HR, hazards ratio; CI, confidence interval.

that this particularly happens when circulatory arrest more than 60 minutes, regardless of cerebral protection. When circulatory arrest time is greater than 60 min, there is a two-fold increase in the risk of mortality (3).

Our study documented a higher mortality with CPB time of greater than 200 minutes (OR=4.7, 95% CI, 1.962–1.072, P=0.029). This represents patients who required more complex aortic reconstruction such as total arch replacement. More complex reconstructions were more frequently performed using ACP, as reported in previous studies (4). In our study, ACP was associated with a longer CPB time, which has also been supported in the literature (5-7). The use of ACP for longer surgeries has been shown to minimize global ischemia and extend the safe HCA time (8,9). When a complex aortic reconstruction was anticipated, surgeons preferred ACP to RCP or DHCA, similar to previous reports (8,9). In contrast, RCP was the preferred strategy when shorter (<30 min) circulatory arrest times are required and when the brain vessels were atheromatous, as a means of reducing the risk of embolic stroke (8,10,11). Patients repaired using ACP underwent significantly more complex procedures such as total arch replacement which inherently required longer CPB times. Despite this disadvantage, ACP demonstrated the same operative mortality as RCP. With the appropriate selection of cerebral perfusion employed, depending on the type of procedure undertaken, we believe that either ACP or RCP can be effective.

Cerebral protection strategy and risk of stroke

The incidence of stroke (P=0.361) did not differ for patients who underwent surgery for type A aortic dissection with ACP, RCP or DHCA. RCP patients demonstrated a trend towards a higher rate of postoperative stroke that may be attributed to the fact that more patients in the RCP group had a history of cerebrovascular accident. Other studies have also demonstrated no difference between RCP and ACP for postoperative stroke; however, RCP tended to have more cases of transient neurological damage (4,6,12,14). The most important risk factors for stroke are circulatory arrest time over 40 minutes and prolonged CPB time (15). While there was a difference in circulatory arrest times in our study, most notably between DHCA patients (17 min, mean) compared to ACP (31 min, mean) and RCP (36 min, mean), the majority of patients had circulatory arrest times under 40 minutes. Given that there was no difference in the incidence of stroke with all perfusion strategies maintained in a relative range of safety, our data suggests that cerebral perfusion technique alone does not impact the risk of stroke.

Actuarial survival

Most independent predictors of long-term mortality following aortic dissection repair have been attributed to cardiovascular causes such as stroke, myocardial infarction and congestive heart failure. However, at least 50% of deaths following discharge have been attributed to other comorbid conditions and not directly related to the repaired aorta (16). These include older age at presentation, chronic renal failure and hemodynamic instability as significant predictors of long-term mortality (16-19). Similar to the literature, our study found age at time of surgery, hemodynamic instability, postoperative stroke, renal failure and CPB time greater than 200 min to be independent predictors of late mortality (*Table 4*). However, our study found no difference in 5-year survival rates for patients repaired using ACP, RCP or DHCA (*Figure 1*). This corresponds well with the fact that we didn't see any major impact on comorbidities by perfusion technique in the perioperative period as well. Without any major incidence in morbidities associated with method of perfusion strategy, we believe that long-term survival is minimally impacted by cerebral perfusion technique.

Clinical implications

We conducted a multi-institutional observational study to assess the impact of methods of cerebral protection on operative characteristics and short- and long-term outcomes following repair of acute type A aortic dissection. In our study we examined an unselected cohort of patients from five academic institutions. This study compared patients that underwent surgery for type A aortic dissection with DHCA, ACP or RCP and evaluated the outcomes and operative mortality. Operative mortality was not statistically significant and was not shown to differ between the different forms of cerebral protection. The choice of whether to utilize RCP or ACP during hypothermic circulatory arrest is dependent on the extent of the aortic dissection and the patient. Currently, the use of ACP via right axillary cannulation with moderate hypothermia for complex aortic reconstructions is preferable in complex aortic reconstructions, since (I) it allows prevention of cerebral ischemia; (II) can be initiated before the chest is open; (III) provides safe and almost unlimited length in time for cerebral protection; and (IV) the axillary level is less likely to be the site of atheromatous lesions or dissection (4,8,11,20-22). When the expected circulatory arrest time is relatively brief (less than 30 minutes), RCP or DHCA are safe alternative neuroprotective strategies during repair of type A dissection (4,8,14,23,24).

Study limitations

Inherent limitations of a retrospective multi-institution investigation inevitably affected our study. Bias may have also been introduced into the analysis since different surgeons from five different institutions performed the procedures. Selection bias may affect the results and it may be possible that the results regarding each neuroprotection strategy may reflect the results of the surgeon performing the operation. Although the duration of cerebral perfusion time is not provided in our study, the duration of cerebral perfusion was almost equivalent to the duration of circulatory arrest time for the ACP and RCP groups. The small sample size was another limitation of our study that did not allow propensity score matching between the three groups to identify differences. Further study of reoperations on the remaining dissected aorta, the differences in outcomes based on use of unilateral or bilateral ACP and the fate of the false lumen were outside the scope of our analysis. In future, these should be the focus for evaluating long-term outcomes of acute type A aortic dissection repair.

Conclusions

The use of cerebral protection during surgical repair of type A aortic dissection should be evaluated on a case-by-case basis dependent on the preoperative patient conditions, complications that occur during surgery and surgical procedures performed. Our findings suggest that during surgical repair of type A aortic dissection, ACP, RCP or DHCA have acceptable morbidity and mortality in selected patients. The presence of hemodynamic instability prior to surgery and prolonged CPB time increases the risk of early and late mortality regardless of cerebral protection strategy.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The study was approved by the Institutional Review Boards of each center. Consistent with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), patient confidentiality was consistently maintained.

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