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Optimal Cerebral Protection Strategies in Aortic Surgery

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Abstract

Cerebral protection strategies in aortic surgery have undergone significant evolution over the years, but its tenets remain rooted in maintenance of hypothermia and cerebral perfusion to limit adverse neurologic outcomes. While deep hypothermic circulatory arrest alone remains a viable approach in many instances, the need for prolonged duration of circulatory arrest and increasing case complexity have driven the utilization of adjunctive cerebral perfusion strategies. In this review, we present the most recent studies published on this topic over the last few years investigating the efficacy of deep hypothermic circulatory arrest, retrograde cerebral perfusion, and unilateral and bilateral antegrade cerebral perfusion, as well as the emerging trend toward mild and moderate HCA temperatures. We highlight the ongoing controversies in the field that underscore the need for large-scale randomized trials using well-defined neurologic endpoints to optimize evidence-based practice in cerebral protection.

Graphical Abstract

Kaplan-Meier survival curve for all-comers undergoing aortic arch surgery using antegrade cerebral perfusion and moderate hypothermic circulatory arrest (28°C).

Keywords

Cerebral protection; deep hypothermic circulatory arrest; moderate hypothermic circulatory arrest; antegrade and retrograde cerebral perfusion

Aortic arch reconstructions are complex procedures mandating a period of circulatory arrest and cerebral ischemia which ultimately increases the risk of adverse neurologic outcomes. Among patients undergoing aortic arch surgery in the current era, permanent stroke is reported to occur in up to 12% and significant cerebral dysfunction in up to 25%.[1] Postoperative permanent neurologic dysfunction (PND) is defined as the presence of new focal (stroke) or global (coma) cerebral dysfunction confirmed on neuroimaging, and temporary neurologic dysfunction (TND) is the presence of reversible confusion, agitation, delirium, or motor deficit with negative radiographic evidence of cerebral injury.[2] Preventing neurologic complications during aortic arch surgery is achieved primarily through use of hypothermia and an adjunctive method of cerebral perfusion to reduce the brain's metabolic

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demand and safely extend the ischemic period. Although cerebral protection strategies have undergone significant evolution in recent years, the optimal strategy remains undefined.

Since the initial description in 1975 of performing total arch replacements using deep hypothermic circulatory arrest (DHCA) at <18°C,[3] it has been shown that the safe period of DHCA without an additional protective adjunct is around 30 minutes while beyond 50 minutes, cellular anoxia and injury occur with significantly increased rates of neurologic dysfunction.[4] Attempts to further improve upon DHCA as a method of cerebral protection during arch reconstruction led to the development of additional protective adjuncts that include both retrograde (RCP) and antegrade cerebral perfusion (ACP). These methods provide a form of continuous brain perfusion used in conjunction with DHCA, and allow for complex arch reconstruction requiring prolonged periods of HCA to be performed safely with lower rates of cerebral injury compared to DHCA alone.

In the current era of aortic arch reconstruction, both RCP and ACP have been shown to be safe and relatively equivalent in preventing neurologic injury for patients undergoing arch replacement. However, the majority of these reports involve single institutional strategies, typically evaluated in a retrospective manner, and thus, the optimal strategy remains debated. Additional discrepancies exist regarding the use of unilateral (u-ACP) vs bilateral (b-ACP) antegrade cerebral perfusion and the optimal temperature of HCA with a trend toward mild or moderate temperatures (MHCA). This review summarizes key findings from 5 studies published since 2016 examining these controversial topics and discusses the implications on cerebral protection strategies in contemporary aortic arch surgery.

FAVORABLE LATE SURVIVAL AFTER AORTIC SURGERY UNDER STRAIGHT DEEP HYPOTHERMIC CIRCULATORY ARREST

Damberg et al[5] report the late-term outcomes for aortic arch surgery using DHCA as an isolated method of cerebral protection and identify variables associated with late survival (follow-up extending up to a mean of 3.8 ± 3.4 years). The authors identified a cohort of 613 patients (mean age: 63.7 years) undergoing aortic surgery with DHCA between 2003 and 2015, including 77.3% hemiarch replacement and 20.4% arch replacement. The indication was aortic aneurysm in 84.8% of cases although 13.1% had aortic dissections, and 23.5% had extension into the descending aorta. Of the entire cohort, 13.7% of operations were performed on an urgent or emergent basis. The mean duration of DHCA for the entire cohort was 29.7 ± 8.5 minutes with 85.5% of patients <40 minutes and 3.1% >50 minutes. Patients were cooled to a target bladder temperature of 20°C for hemiarch or 18°C for total arch replacement.

Stroke rate was 2% among the entire cohort and was significantly higher in patients with DHCA times >50 minutes (10.5%, $P = 0.05$). TND rate was 5.1%. Operative mortality was 2.9% and differed based on type of procedure. Patients undergoing elective first-time surgery in nondissection cases ($n = 424$) had similar survival compared to those of the normal reference population (standardized mortality ratio: 1.242; 95% confidence interval 0.93–1.65; Fig. 1). Survival was better for those undergoing surgery for aneurysmal disease vs

dissection as well as hemiarch vs total arch replacement. Overall survival among the entire cohort was 92.2% at 1 year and 81.5% at 5 years.

Acute type A aortic dissection (hazard ratio [HR] 4.84; $P = 0.000$), redo status (HR 4.12; $P = 0.000$), and presence of descending aortic pathology (HR 5.54; $P = 0.000$) were independently associated with reduced early survival within the first postoperative year. After 1 year, age (HR 1.07; $P = 0.000$), major complications (HR 3.11; $P = 0.000$), and atrial fibrillation (HR 2.47; $P = 0.0006$) were independently associated with poor survival. DHCA duration was not significantly associated with poor survival on multivariable analysis.

These results indicate that for low-risk patients (ie, undergoing elective, nondissection, first-time operations), aortic arch reconstruction with DHCA alone can be performed with favorable late survival. The lack of any significant association between DHCA time and late survival suggests that any subtle brain damage possibly caused by DHCA has a limited effect on late survival. However, as nearly 90% of patients underwent DHCA duration <40 minutes, the authors caution that these results may not be generalizable for those with prolonged DHCA duration >50 minutes when other perfusion methods may be preferable.

RETROGRADE CEREBRAL PERFUSION IS EFFECTIVE FOR PROLONGED CIRCULATORY ARREST IN ARCH ANEURYSM REPAIR

In this study, Lau et al[6] evaluate whether adjunctive RCP use provides adequate brain protection for prolonged periods of DHCA among a cohort of 1043 patients undergoing aortic arch operations between 1997 and 2014. All patients received RCP in addition to DHCA at 18°C. Of these, 993 patients had DHCA duration <50 minutes (<50 mean: 24.2 ± 8.8 minutes) and 50 had duration ≥50 minutes (≥50 mean: 58.2 ± 8.2 minutes). In this latter group, the majority (94%) underwent total arch vs hemiarch replacement and were more likely to have an aortic dissection, previous stroke, and a prior cardiac operation. The authors therefore performed a propensity-matched analysis between these 2 groups resulting in 48 pairs (mean age: 65.7 ± 13.3 years) and identified predictors of operative death and postoperative cerebral complications.

Of the entire cohort, PND occurred in 13 (1.2%) and TND in 33 patients (3.2%). In the unmatched population, there was no difference in rate of PND between the ≥50 and <50 groups (2% vs 1.2%, $P = 0.623$) although the rate of TND was significantly higher in the ≥50 group (8% vs 2.9%, $P = 0.045$). Overall mortality was 8% in the ≥50 group and 3.8% in the <50 group ($P = 0.143$).

After matching, rates of operative death (2.1% vs 0.0%, $P = 0.315$) and postoperative complications including incidence of TND (6.3% vs 2.1%, $P = 0.307$) and PND (2.1% vs 0.0%, $P = 0.315$) were similar in the ≥50 minutes and <50 minutes groups, respectively. The 3-year and 5-year survival in the overall population were 78.8% and 67.8% and were not significantly different between groups (Fig. 2).

Age, previous myocardial infarction, cardiopulmonary bypass (CPB) time, and need for intraoperative blood transfusion were independent predictors of operative death. The need

for total arch replacement and DHCA duration were not independently associated with operative death or postoperative outcomes. The authors conclude that use of RCP in this setting is not associated with increased death or adverse neurologic outcomes. These findings provide support for RCP as an effective adjunctive cerebral protection strategy for complex aortic arch aneurysm repair with prolonged DHCA.

THE STANDARDIZED CONCEPT OF MODERATE-TO-MILD (≥28°C) SYSTEMIC HYPOTHERMIA DURING SELECTIVE ANTEGRADE CEREBRAL PERFUSION FOR ALL-COMERS IN AORTIC ARCH SURGERY: SINGLE-CENTER EXPERIENCE IN 587 CONSECUTIVE PATIENTS OVER A 15-YEAR PERIOD

Ahmad et al[7] describe their 15-year institutional experience with use of moderate-to-mild systemic hypothermia (MHCA) with adjunctive selective ACP for patients undergoing aortic arch operations since implementation of a standardized perfusion and temperature management protocol in 2000.

Between 2000 and 2015, 587 consecutive patients (mean age: 68 ± 16 years) underwent aortic arch reconstructions at a single institution using adjunctive ACP with mean HCA temperature of 28.7 ± 0.6°C and duration of 48 ± 21 minutes. Of these, 393 underwent unilateral ACP (u-ACP: 67%), and 194 underwent bilateral ACP (b-ACP: 33%). Two hundred nineteen patients (37%) presented with acute type A aortic dissection, and 56 (10%) had a prior aortic arch procedure. Hemiarch replacement was performed in 386 patients (66%) and total arch replacement in 201 (34%).

ACP was delivered at 30°C using a pressure-controlled protocol with flows of 1.2 ± 0.3 L/min. Notably, the authors state that b-ACP was their strategy of choice between 2005 and 2009. After 2010, u-ACP was favored with b-ACP reserved for patients who experienced a decrease of cerebral oxygen saturation as assessed by near-infrared spectroscopy measure ment below 75% of baseline after initiation of u-ACP.

New postoperative PND occurred in 34 patients (6%) with 33 experiencing stroke and 1 experiencing paraplegia. TND occurred in 29 patients (5%). The incidence of PND (5% vs 7%, $P = 0.180$) and TND (5% vs 6%, $P = 0.220$) did not differ between patients receiving u-ACP vs b-ACP, respectively. The 30-day mortality was 6%. Kaplan-Meier survival estimates were 94 ± 2% at 1 year, 87 ± 4% at 5 years, and 69 ± 6% at 10 years (Fig. 3). Renal failure requiring renal replacement therapy occurred in 49 patients (8%) and permanent renal failure in 12 (2%).

The authors conclude that selective ACP in combination with moderate-to-mild systemic hypothermia provides sufficient neurologic and visceral organ protection to all-comers requiring aortic arch surgery without pathologic or procedural limitations.

BILATERAL VERSUS UNILATERAL ANTEGRADE CEREBRAL PERFUSION IN TOTAL ARCH REPLACEMENT FOR TYPE A AORTIC DISSECTION

In this study, Tong et al[8] directly compare clinical outcomes in the use of b-ACP vs u-ACP for type A aortic dissection.

The authors identified 203 patients (median age: 51.0 ± 13 years) presenting with acute type A aortic dissection undergoing total aortic arch replacement at their institution between 2006 and 2014. ACP was used for all patients with 82 (40.3%) undergoing u-ACP and 121 (59.7%) undergoing b-ACP. The authors note that they targeted a nasopharyngeal temperature of 24°C in the beginning of their series, which was increased to 26°C toward the end of the study period. In the b-ACP group, cerebral perfusion was performed via the right axillary artery and left common carotid artery with flow of 10–15 mL/kg/min and perfusion pressure of 40–50 mm Hg. In the u-ACP group, right axillary artery cannulation was performed for CPB and delivery of ACP.

The durations of CPB time, cross-clamp time, and circulatory arrest time were 198 ± 53 minutes, 101 ± 36 minutes, and 24 ± 8 minutes, respectively, and were similar between groups. For the entire cohort, the mortality rate was 14.5%. Overall 30-day mortality was comparable in the 2 groups (11.6% for b-ACP vs 20.7% for u-ACP, $P = 0.075$; Fig. 4). Prevalence of TND (9.2% vs 4.7%, $P = 0.236$) and PND (16.9% vs 8.4%, $P = 0.091$) were similar in the u-ACP and b-ACP groups, respectively. However, b-ACP was associated with a shorter mean ventilation time (95.5 ± 45.25 hours vs 147.0 ± 82 hours, $P < 0.010$) and lower tracheostomy rate compared to u-ACP.

CPB and circulatory arrest time were independent risk factors for both mortality and PND. Although it is not explicitly stated why one perfusion strategy was chosen over the other over the course of their study, the authors did not find an increase in duration of CPB, cross-clamp, and circulatory arrest with use of b-ACP compared to u-ACP. They conclude that b-ACP did not result in significantly lower 30-day mortality or PND rates compared with use of u-ACP in the setting of acute type A aortic dissection.

DEEP HYPOTHERMIA + RETROGRADE CEREBRAL PERFUSION VERSUS MODERATE HYPOTHERMIA + ANTEGRADE CEREBRAL PERFUSION FOR ARCH SURGERY

Leshnower et al[9] conduct a prospective randomized controlled trial comparing two well-established neuroprotective strategies in patients undergoing elective transverse hemiarch replacement.

Twenty patients (mean age: 57 ± 12 years) at a single institution were prospectively randomized to DHCA + RCP ($n = 11$, mean temperature: 19.9 ± 0.1°C) vs MHCA + ACP ($n = 9$, mean temperature: 26.3 ± 1.8°C). The primary endpoint was defined as the composite of stroke, transient ischemic attack, and magnetic resonance imaging (MRI) evidence of brain injury. Secondary endpoints were TND, neurocognitive deficits as assessed by central

nervous system vital signs and serum S-100 levels, a nonspecific biomarker for neuronal injury. Patients in the DHCA + RCP group underwent bicaval cannulation. RCP was delivered at 1°C at a rate of 300–500 mL/min to achieve a pressure of 20–25 mm Hg. In the MHCA + ACP group, ACP was delivered via the right axillary artery with clamp occlusion of the innominate and left common carotid arteries during circulatory arrest.

The authors found no differences in CPB, cross-clamp, or circulatory arrest times between the 2 groups. All patients received neurologist-adjudicated exams and brain MRIs prior to discharge. Postoperative National Institute of Health Stroke Scale scores and neurocognitive test results were equivalent between groups. There was 1 confirmed stroke in each group, and 2 patients in the MHCA + ACP group experienced TND that resolved by hospital discharge. However, diffusion- weighted imaging (DWI) MRI demonstrated lesions in 100% (9/9) of MHCA + ACP patients compared to 45% (5/11) of DHCA + RCP patients ($P < 0.010$). Additionally, the number of DWI lesions was significantly higher in the MHCA + ACP vs DHCA + RCP group (4 ± 3.5 vs 1.2 ± 2.1, $P < 0.010$) with the most common area of lesions in the frontal lobes bilaterally (Table). There were no cases of renal failure, respiratory failure, or mortality among the entire cohort.

Although there were no significant differences in clinically evident neurologic injury between the DHCA + RCP and MHCA + ACP groups, these findings demonstrate that the latter strategy may be associated with a higher incidence of radiographic neurologic injury. Moreover, the pattern of brain injury is consistent with embolic phenomena rather than ischemic damage due to hypoperfusion. Although the authors note that this pilot study is limited by a lack of power, and the clinical significance of these silent infarcts remains unclear, they support a larger randomized clinical trial to evaluate these 2 neuroprotective strategies previously thought to be equivalent.

COMMENTARY

Cerebral protection strategies in aortic surgery have undergone significant evolution over the last few decades, but the optimal method remains controversial. A recent analysis of the STS Adult Cardiac Surgery Database of >12,000 aortic arch repairs with HCA between 2011 and 2014 found significant variability in temperature and perfusion strategies with the most common being straight DHCA (25%), DHCA + RCP (16%), and DHCA + ACP (14%).[10] Although this report included both high-volume and less-experienced centers, it indicated that the lack of a protective adjunctive strategy for cerebral perfusion may result in a higher risk of mortality or adverse neurologic complications compared to HCA alone (odds ratio 1.6, $P < 0.01$).

However, as shown by Damberg et al,[5] excellent outcomes can be achieved with straight DHCA for periods of up to 40 minutes. The Yale group has had extensive experience with this technique, and in their series of all-comers undergoing straight DHCA, favorable late-term outcomes were reported. In particular, patients presenting for elective, non-dissection, first-time operations had similar survival compared to that of an age- and sex-matched reference group. The incidence of adverse neurologic outcomes, including a 2% stroke and 5.1% TND rate, compares favorably to out-comes in other series utilizing adjunctive

cerebral protection strategies. These results suggest that the subclinical lesions thought to be caused by DHCA may have a limited impact on late-term survival. Although there was no association between DHCA duration and survival in this study, the comparatively small numbers of patients undergoing DHCA >50 minutes preclude generalizing these findings to prolonged durations of HCA, at which point, adjunctive cerebral perfusion strategies are necessary.

The pursuit of additional adjuncts for cerebral protection led to the development of RCP and ACP. The proposed strengths of RCP are its ability to maintain cold cerebral temperatures and efficacy in washing out particulate and gaseous emboli from the cerebrovasculature. Proponents argue that it provides an uncluttered field and avoids potential injury from arterial cannulation. Lau et al[6] present their data on DHCA + RCP for patients undergoing DHCA duration <50 minutes vs ≥50 minutes and found no difference in major postoperative complications including death, TND, and PND. Although propensity matching only yielded 48 pairs, they make a convincing case that in an experienced center, RCP can be a safe and effective adjunct for complex aortic arch reconstruction with prolonged DHCA.

While the study by Lau et al supports the literature, which has demonstrated equivalent neuroprotection between RCP and ACP, there is growing consensus among aortic surgeons that ACP is the preferred method of cerebral perfusion for extended HCA times. ACP is thought to provide more physiologic delivery of blood flow that facilitates cerebral metabolism and preservation of cell architecture. Driven by recent data supporting safety and equivalent neurologic outcomes, the emerging trend is toward warmer temperatures of HCA to moderate (20.1–28°C) and mild (28.1–34°C). This is accentuated by the desire to decrease hypothermia-induced multiorgan dysfunction including coagulopathy, transfusion requirements, and CPB and operative duration.

Ahmad et al[7] demonstrate the versatility and feasibility of ACP in combination with moderate-to-mild systemic HCA (28.7 ± 0.6°C) among all-comers presenting for aortic arch surgery over a 15-year period. The low overall 30-day mortality, PND, and TND rates of 6%, 6%, and 5%, respectively, for elective and emergent cases encompassing a range of complexi ties highlight the efficacy of their institutional, standardized protocol for perfusion and temperature management.

In the current era of ACP, there is no consensus on whether u-ACP or b-ACP offers superior cerebral perfusion with the decision remaining surgeon preference. In the setting of MHCA, b-ACP is thought to provide improved bihemispherical cerebral perfusion, but there may be an added risk of arch vessel manipulation over u-ACP. Tong et al[8] add to the growing body of literature demonstrating equivalent outcomes between u-ACP vs b-ACP for aortic arch surgery by focusing on patients presenting with acute type A aortic dissection and undergoing total arch replacement. Use of b-ACP did not increase cross-clamp, CPB, or overall operative duration. While only u-ACP was used early on in their series, the authors used either u-ACP or b-ACP in the latter half of their study period. No specific rationale is given for why one was chosen over the other, but it may be reasonable to start with u-ACP in patients who have no prior neck vessel pathologies, demonstrate sufficient backflow from the contralateral carotid artery, and exhibit no evidence of cerebral malperfusion on

intraoperative near-infrared spectroscopy assessment. In contrast, b-ACP may be more favorable in patients who have had a prior stroke, significant carotid artery stenosis, or evidence of cerebrovascular anomalies such as an incomplete Circle of Willis.

A major limitation to establishing an optimal cerebral perfusion strategy for aortic surgery is the lack of randomized clinical trials. Moreover, most studies have relied on only clinical neurologic endpoints rather than neuropsychological testing or radiographic imaging analysis, which may be more sensitive indicators of neurologic injury.[11]

Leshnower et al[9] present the results of a pilot study comparing outcomes among a low-risk patient cohort undergoing elective ascending aortic aneurysm repair under DHCA + RCP vs MHCA + ACP. Although there were no differences in clinically evident neurologic injury with only 1 patient in each group suffering a stroke, all patients receiving MHCA + ACP had MRI DWI lesions compared to less than half of those receiving DHCA-RCP. Additionally, the number of lesions was significantly higher in the MHCA + ACP group. Although power was a limiting factor in this pilot study, and the significance of these clinically silent lesions is unclear, these findings challenge the belief that MHCA + ACP and DHCA + RCP produce equivalent neuroprotection in patients undergoing limited arch reconstruction.

In summary, since the initial description of DHCA in the management of aortic arch pathology, the field of aortic surgery has undergone significant advances. However, there remains great variability in institutional practice, and controversies persist regarding the optimal strategy for cerebral protection. Although this review of the most recent papers published on this topic offers some insight into emerging trends in the field, no single strategy has been proven to be superior, and many unanswered questions remain. Such controversies are perhaps reflective of the high complexity of aortic arch operations and their associated morbidity and mortality. Importantly, they emphasize the growing need for large-scale randomized clinical trials stratified by case complexity, type, and acuity to address these ongoing areas of dispute. It is imperative that such trials incorporate the use of radiographic imaging and neuropsychological testing to adjudicate neurologic injury rather than rely solely on clinical observation. By employing such an evidence-based strategy built on interdisciplinary and multi-institutional investigational collaboration, perhaps further improvements in outcomes in aortic arch surgery can ultimately be achieved.

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Central Message

Despite significant advances in recent years, optimal cerebral protection strategies in aortic surgery remain controversial, emphasizing the need for randomized clinical trials to guide best practice.

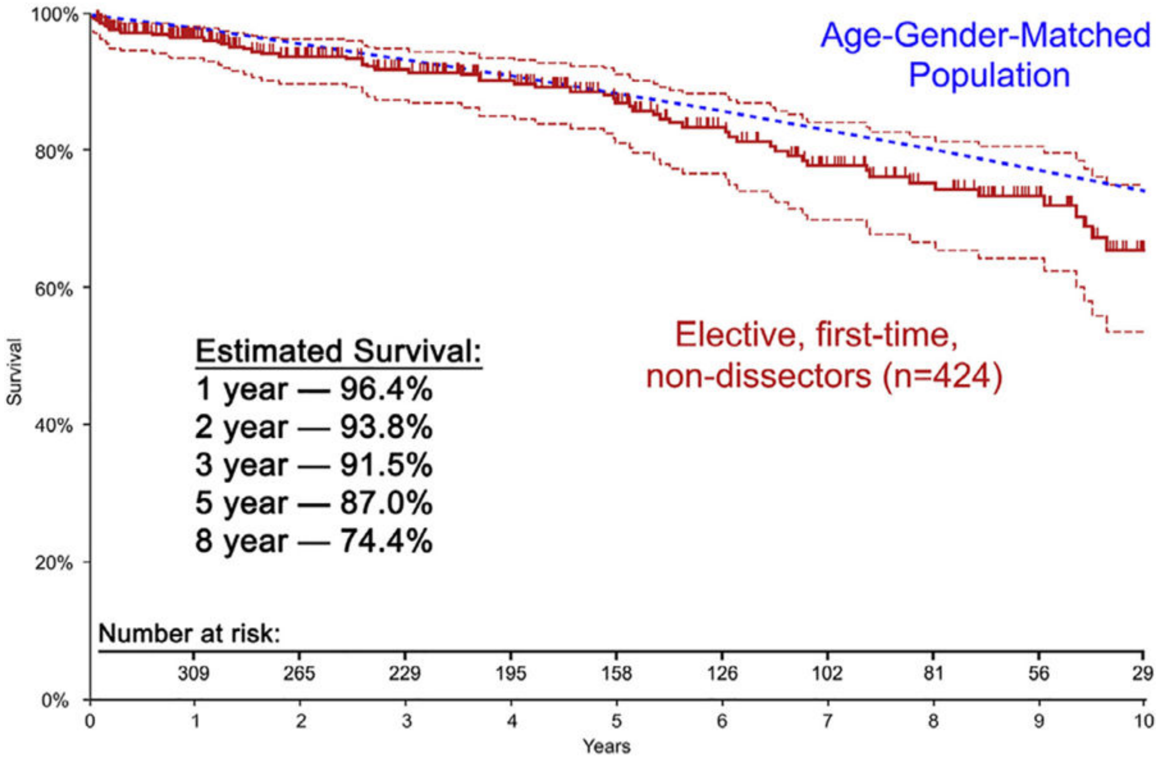

Figure 1.

Kaplan-Meier survival analysis comparing elective, first-time nondissection cases (n =424) with a reference population. Rug marks represent censored patients; dotted lines represent confidence bands. The survival of this group of DHCA patients was not significantly different from the age- and sex-matched population. (Adapted with permission Damberg et al.[5])

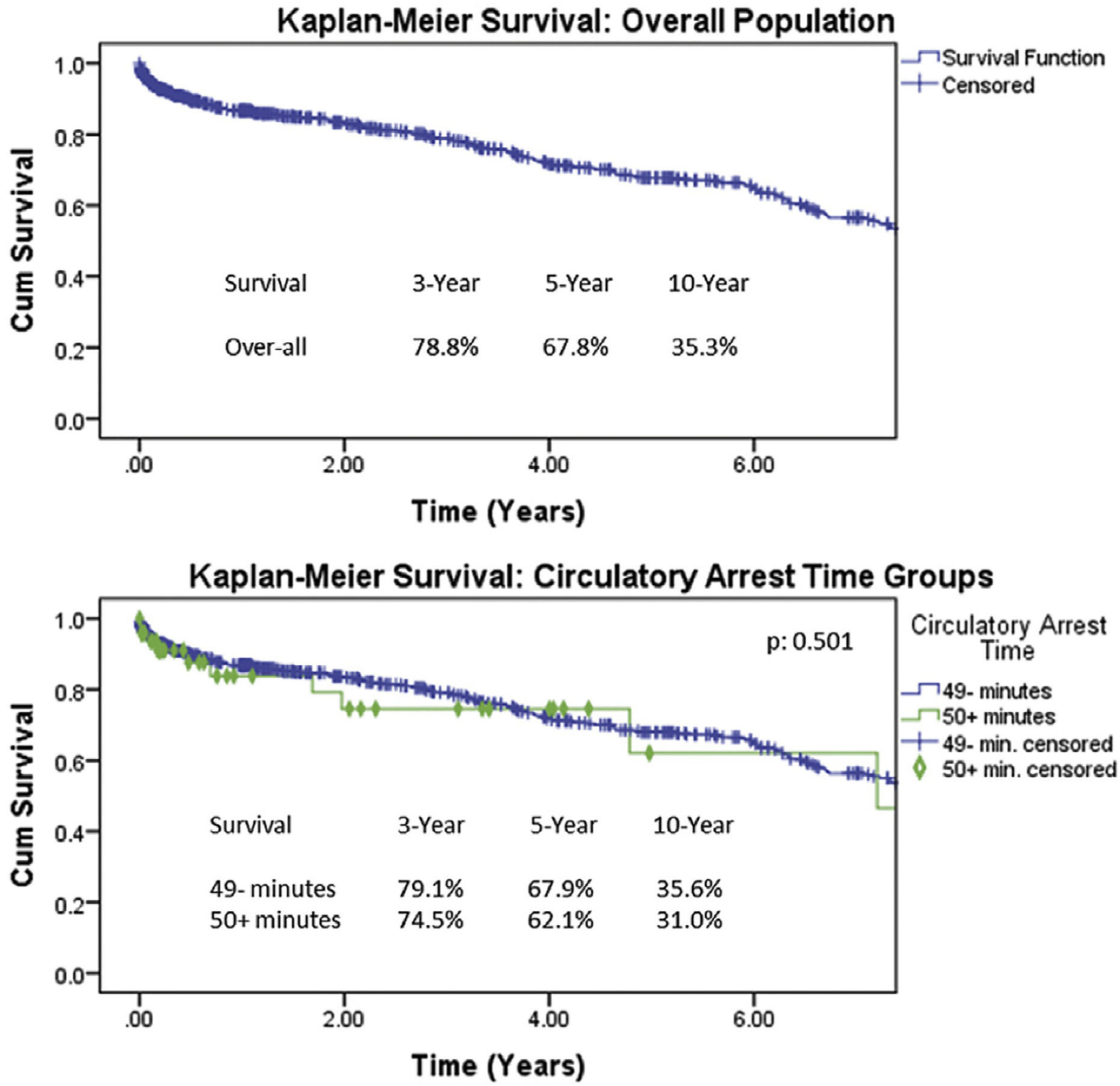

Figure 2.

Kaplan-Meier survival estimates (top) for all-comers undergoing DHCA + RCP and (bottom) broken down by groups based on duration of DHCA. (Adapted with permission Lau et al.[6])

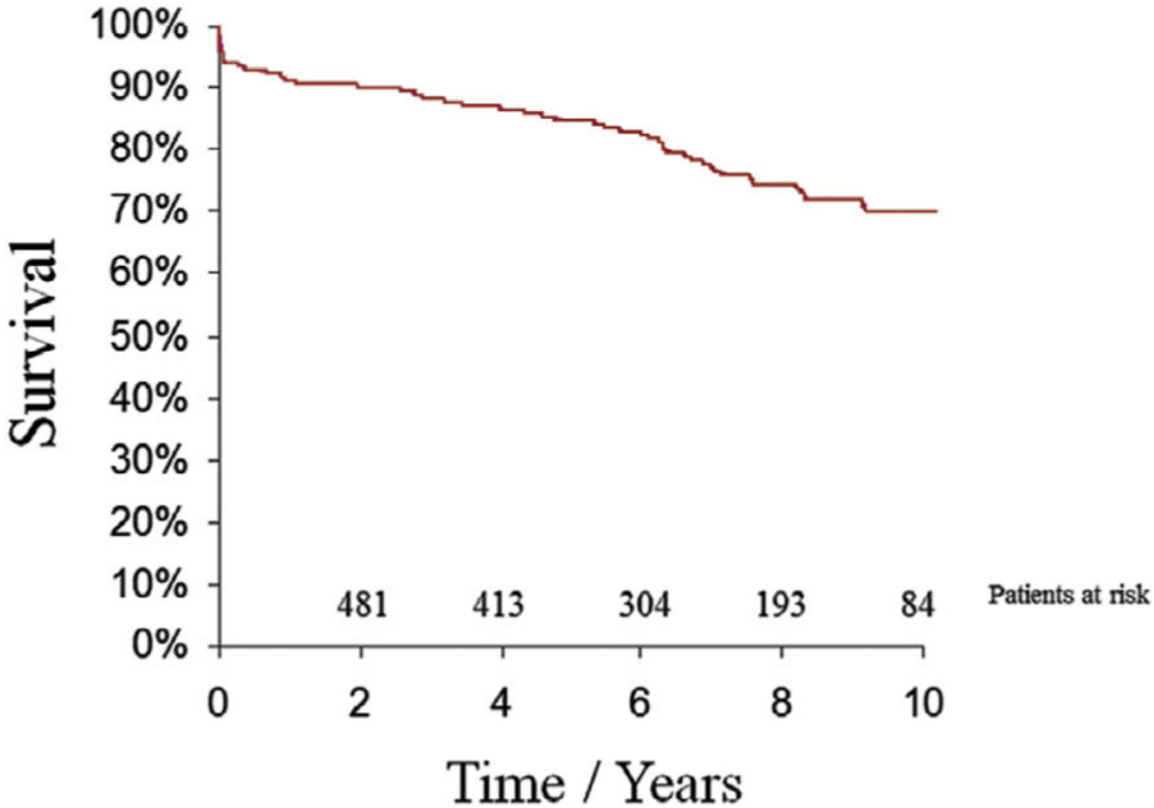

Figure 3.

Kaplan-Meier survival curve for all-comers undergoing aortic arch surgery using ACP and MHCA (≥28°C). The number of patients at risk is indicated. (Adapted with permission Ahmad et al.[7])

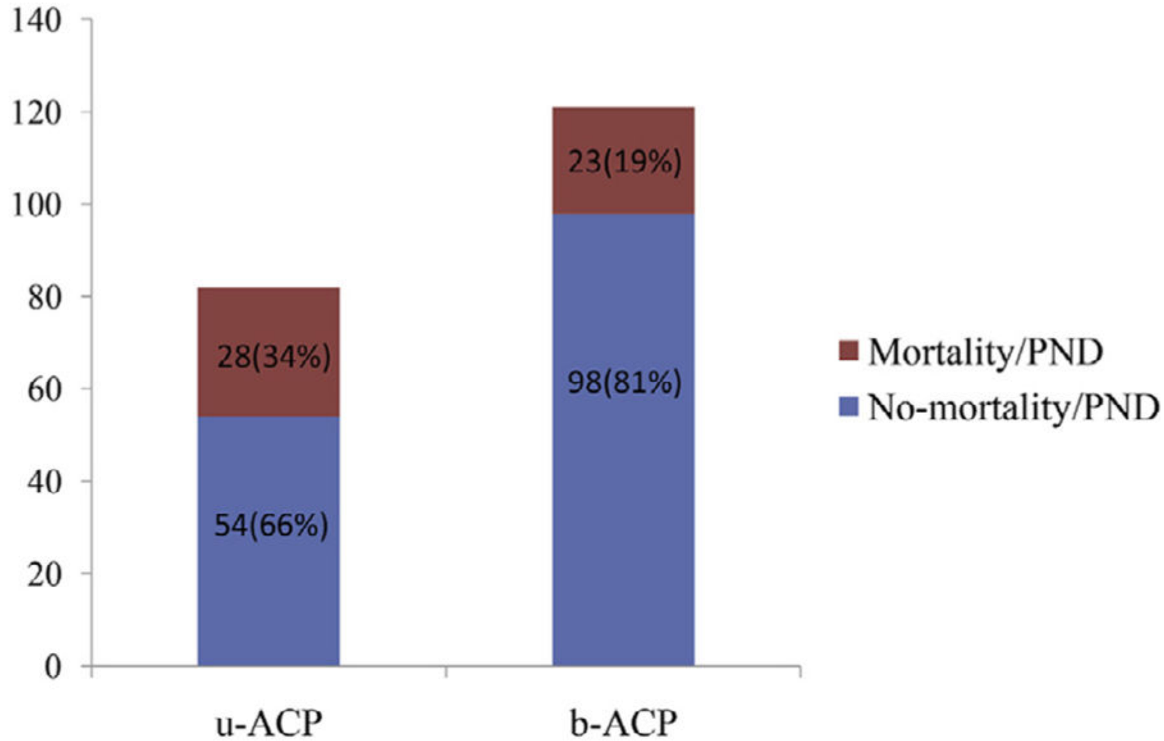

Figure 4.
Thirty-day mortality and incidence of PND in the u-ACP ($n = 82$) and b-ACP ($n = 121$) groups among patients presenting with type A aortic dissection undergoing total arch replacement with selective ACP and MHCA. (Adapted with permission Tong et al.[8])

Table

Neurologic Outcomes Among a Low-Risk Patient Cohort Undergoing Elective Ascending Aortic Aneurysm Repair Randomized to DHCA + RCP or MHCA + ACP. (Adapted with permission Leshnower et al.[9])

	DHCA + RCP (*n* = 11)	MHCA + ACP (*n* = 9)	*P*
Composite of stroke, TIA, MRI DWI lesions	5 (45%)	9 (100%)	0.01 *
Stroke	1 (9%)	1 (11 %)	0.28
TND	0	2 (22%)	0.19
TIA	0	0	1
S-100 POD #1	123 ± 66	132 ± 58	0.77
S-100 POD #3	62 ± 38	67 ± 46	0.79
S-100 POD #7	53 ± 34	49 ± 24	0.66
Patients with MRI DWI lesions	5 (45%)	9 (100%)	0.01 *
Number of DWI lesions	1.2 ± 2.1	4 ± 3.5	0.01 *
Volume of DWI lesions (cc)	0.54 ± 0.72	1.29 ± 3.01	0.63

DWI, diffusion weight imaging; MRI, magnetic resonance imaging; POD, postoperative day; TIA, transient ischemic accident; TND, transient neurologic dysfunction.

All data are mean ± SD or *n* (%).

* $P < 0.05$.