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# Neurologic Dysfunction after Aortic Dissection Surgery: Different Cerebral Hypothermic Antegrade Perfusion Techniques

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## Abstract

**Introduction:** Neurologic dysfunction remains one of the most disabling complications of emergency aortic arch surgery. Many cerebral protection techniques are described, but their comparison has always been hampered by the wide spectrum of preoperative conditions, pathologic anatomies, complications, and surgical procedures. The aim of our study was to evaluate the incidence of early permanent neurologic injury and in-hospital mortality after emergency aortic arch surgery splitted by different antegrade cerebral perfusion techniques combined with hypothermic circulatory arrest (HCA).

**Methods:** Between January 2005 and December 2015, 249 patients underwent emergent surgery for acute, type A aortic dissection. Of these, 112 (45%) (Mean age 63.8 ± 12.8 years, 82 males) received cerebral protection through antegrade perfusion of the supra-aortic vessels. Unilateral perfusion (UACP) was performed in 55 (49.1%) patients, while bilateral perfusion (BACP) was achieved *via* right axillary artery cannulation alone in 25 (22.3%) cases or with the Kazui technique in 32 (28.6%). Permanent neurologic injury was defined as the post-operative onset of focal stroke or lethal coma.

**Results:** In-hospital mortality was 17.9% (UACP 20% *vs.* BACP 15.8%; p=0.56). The global rate of the early permanent neurologic injury was 12.3% (UACP 10.9% *vs.* BACP 15.8%; p=0.45).

**Conclusion:** There is no evidence that BACP combined with HCA is superior to UACP combined with HCA for emergency aortic arch surgery in preventing early permanent neurologic injury and in-hospital mortality.

**Keywords:** Aortic arch surgery; Neurologic injury; Cerebral perfusion; Acute aortic dissection

## Introduction

Acute type A aortic dissection (AAAD) is a life-threatening condition and a real challenge for cardiac surgeons. Its prevalence ranges between 0.5 and 4 cases per 100.000 people per year [1]. The mortality for untreated AAAD is 50% in the first 24 h and 75% within 2 weeks after onset [2]. Although early referral of patients for surgery, improved surgical techniques and preoperative care, in-hospital mortality following surgical treatment still remains high, ranging from 10 to 30% [3-6].

Neurologic dysfunction remains one of the most significant and disabling complications of aortic arch surgery, often leading to death. Its incidence ranges between 5.5% and 33.3%, depending on the extent of replaced aorta, age, urgency of surgery, and strategies of brain protection [7].

To protect the brain and reduce cerebral complications, various cerebral protection techniques have been suggested, such as deep hypothermic circulatory arrest (deep HCA), retrograde cerebral perfusion (RCP), or antegrade cerebral perfusion (ACP) [8-10].

Comparison of these different strategies of cerebral protection has always been hampered by the wide spectrum of preoperative conditions, pathologic anatomies, complications, and surgical procedures. Thus, conclusive evidence is still lacking and there is no consensus concerning the optimal method for cerebral protection.

The aim of the present study was to report our clinical experience of cerebral protection strategies, and to evaluate the incidence of early permanent neurologic injury (PNI) and in-hospital mortality after emergency aortic arch surgery for AAAD splitted by different ACP techniques, combined with moderate HCA.

## Methods

This was a single-center, observational, retrospective study. The endpoint was to compare the incidence of early PNI and the in-hospital mortality after emergency aortic arch surgery for AAAD, following different two ACP techniques, i.e. bilateral (BACP) and unilateral (UACP), combined with HCA. Study approval was granted by the Ethics Committee of the Tor Vergata University Hospital of Rome. Between January 2005 and December 2015, 249 patients (range 16-87 years, mean age 63.0 ± 12.9 years, 175 males) underwent emergent surgery for AAAD [11].

The exclusion criteria were the following: 1) selective cerebral perfusion not needed; 2) intra-operative deaths; 3) preoperative onset of neurologic symptoms and/or imaging evidence (i.e. absence of organ perfusion at CT-angiography) of cerebral malperfusion also confirmed after surgery.

Therefore, 112/249 patients (45%) (Range 16-87 years, mean age 63.8 ± 12.8 years, 82 males) could be enrolled. The demographic and clinical characteristics of the study population are summarized in Table 1.

| | Total n=112 | UACP n=55 | BACP n=57 | p-value (UACP *vs.* BACP) |
|---|---|---|---|---|
| Age (years), mean ± SD | 63.8 ± 12.8 | 62.7 ± 13.8 | 64.8 ± 11.8 | 0.39 |
| Male sex, n (%) | 82 (73.2) | 41 (74.5) | 41 (71.9) | 0.75 |
| Clinical history, n (%) | | | | |
| Hypertension | 98 (87.5) | 45 (81.8) | 53 (93.1) | 0.07 |
| Smoke habit | 32 (28.6) | 14 (25.4) | 18 (31.6) | 0.47 |
| BMI (Kg/m$^2$)>30 | 22 (19.6) | 11 (20.0) | 11 (19.3) | 0.93 |
| History of CAD | 6 (5.4) | 3 (5.5) | 3 (5.3) | 0.99 |
| Previous cardiac surgery | 5 (4.5) | 2 (3.6) | 3 (5.3.0) | 0.99 |
| Dialysis-dependent renal failure | 1 (0.9) | 0 | 1 (1.7) | 0.99 |
| Entry tear aortic dissection, n (%) | | | | |
| Ascending aorta | 59 (52.7) | 28 (50.9) | 31 (54.4) | 0.71 |
| Aortic arch | 29 (25.9) | 15 (27.3) | 14 (24.6) | 0.74 |
| Descending aorta | 5 (4.5) | 2 (3.6) | 3 (5.3) | 0.99 |
| Unknown | 19 (17.0) | 10 (18.2) | 9 (15.8) | 0.74 |

**Table 1:** Preoperative characteristics. BMI: Body Mass Index; CAD: Coronary Artery Disease; SD: Standard Deviation.

We defined in-hospital mortality as any death from any cause, occurring within 30 days from surgery or during hospitalization (including transferral to a cardiac rehabilitation facility) regardless of the time elapsed from the operation.

PNI was defined as the presence of post-operative stroke or lethal coma, clinically diagnosed by the neurologist, and instrumentally confirmed by means of cerebral MRI or CT scan.

## Surgical technique

Preoperative monitoring included a Swan-Ganz pulmonary artery catheter, double artery cannulation for continuous arterial blood pressure (i.e. radial, femoral) and body temperature measurement during surgery (rectal and esophageal). Moreover cerebral tissue oxygenation was measured by means of near infrared spectroscopy (INVOS® System, Somanetics Corp., Troy, MI, USA) and transcranial Doppler measurement of blood velocity flow in the middle and/or anterior cerebral artery.

Access to the heart was obtained through a complete median longitudinal sternotomy in all patients. Arterial access for cardiopulmonary bypass (CBP) was *via* femoral artery or right axillary artery or, when a peripheral artery was not accessible, directly through the ascending aorta with the aid of a metallic wire inserted in the true lumen under echographic control. Venous drainage was obtained by means of atrio-caval, bicaval, or atrio-femoral cannulation. The left ventricle was vented through the right superior pulmonary vein or the main pulmonary artery.

After start of the CPB and during patient's cooling, the ascending aorta was cross-clamped and a cold crystalloid cardioplegic solution (Custodiol) was administered directly into coronary ostia. Subsequently, the ascending aorta was inspected in the search for intimal tears and completely resected; aortic valve and coronary arteries were inspected to establish if a proximal extension of aortic replacement was needed. The proximal correction was usually completed during cooling and before HCA.

| | Total n=112 | UACP n=55 | BACP n=57 | p-value (UACP *vs.* BACP) |
|---|---|---|---|---|
| Arterial cannulation, n (%) | | | | |
| Right axillary | 68 (60.7) | 39 (70.9) | 29 (50.9) | 0.03 |
| Right or left femoral | 40 (35.7) | 13 (23.6) | 27 (47.4) | 0.01 |
| Ascending aorta | 4 (3.6) | 3 (5.4) | 1 (1.7) | 0.36 |
| Circulatory arrest temperature (°C), mean ± SD | 27.9 ± 1.7 | 27.4 ± 2.4 | 26.8 ± 1.6 | 0.1 |
| Surgical times (min), mean ± SD | | | | |
| CPB | 180.3 ± 67.3 | 179.8 ± 85.5 | 180.8 ± 43.9 | 0.94 |
| Aortic cross clamp | 99.8 ± 42.9 | 100.1 ± 49.5 | 99.5 ± 35.8 | 0.94 |
| Circulatory arrest | 38.0 ± 26.4 | 39.5 ± 33.1 | 36.6 ± 17.9 | 0.57 |
| Distal extent of aortic procedure, n (%) | | | | |
| Ascending | 22 (19.6) | 14 (25.4) | 8 (14.0) | 0.15 |
| Proximal arch (hemiarch) | 68 (60.7) | 29 (52.7) | 39 (68.4) | 0.1 |
| Arch | 22 (19.6) | 11 (20.0) | 11 (19.3) | 0.93 |
| Concomitant procedures, n (%) | | | | |
| Aortic valve replacement | 8 (7.1) | 6 (10.9) | 2 (3.5) | 0.16 |
| Aortic root replacement | 18 (16.1) | 10 (18.2) | 8 (14.0) | 0.55 |
| Endovascular repair descending aorta | 8 (7.1) | 3 (5.4) | 5 (8.8) | 0.72 |
| Coronary artery bypass | 5 (4.5) | 3 (5.4) | 2 (3.5) | 0.68 |

**Table 2:** Intraoperative variables. CPB: Cardiopulmonary Bypass.

Cerebral perfusion was performed by means of UACP through the right axillary artery, and BACP. Cerebral perfusion was achieved either *via* right axillary artery cannulation alone followed of a side-biting clamping of the top of the aortic arch in a way that the origins of the innominate and left carotid arteries were freely communicating, or with a direct intra-luminal cannulation of the innominate and left common carotid arteries, according with the Kazui technique [10,12,13]. Selective ACP was conducted with a perfusion temperature of 26-28°C in a pressure-controlled way. The perfusion pressure was controlled on pump unit with a perfusion flow of 10 to 15 ml/kg/min to achieve a cerebral perfusion of about 60 mmHg. The aortic arch and proximal descending aorta were explored to identify the site of further intimal tears that were resected whenever possible. Distal aortic repair was achieved using "open technique" and mild-to-moderate hypothermia (≥ 26°C).

After completion of the distal anastomosis, systemic CPB was re-instituted and the re-warming started. In case of total arch replacement, two different vascular prostheses were used, and the two segments were anastomosed at this time point. The proximal anastomosis was performed during this time. Intraoperative data are listed in Table 2.

## Statistical analysis

Analysis was performed with Stat View 4.5 (SAS Institute Inc, Abacus Concepts, Berkeley, CA). Differences between groups were calculated using the Student's t test for continuous data and the $X^2$ or Fisher's exact tests for categorical data. For all statistical analysis a $p<0.05$ was considered significant.

Factors influencing PNI and in-hospital mortality were initially explored by separate univariate analyses with regard to operative and both operative and postoperative variables, respectively. A $p<0.10$ on univariate analyses was considered for entry in multivariable model performed by means of Cox's regression. Odds ratios (OR) are reported with 95% confidence interval value (CI).

## Results

UACP was performed in 55 (49.1%) patients, while BACP in 57 (50.9%) cases. Circulatory arrest with mild-to-moderate hypothermia (27.9 ± 1.7°C) was established in all patients (UACP 27.4 ± 2.4°C *vs.* BACP 26.8 ± 1.6°C, p=0.10).

Arterial access for CBP was mainly *via* femoral artery in BACP group (67.5%, p=0.01) and right axillary artery in UACP group (57.3%, p=0.03). In 4 (3.6%) cases a peripheral artery was not accessible and the arterial access was directly through the ascending aorta (p=0.36).

No differences were found between groups about CPB (UACP 179.8 ± 85.5 min *vs.* BACP 180.8 ± 43.9 min, p=0.94), aortic cross clamp (UACP 100.1 ± 49.5 min *vs.* BACP 99.5 ± 35.8 min, p=0.94) and circulatory arrest time (UACP 39.5 ± 33.1 min *vs.* BACP 36.6 ± 17.9 min, p=0.57).

Similarly, no significant differences were found regarding the distal extension of the aortic repair despite a higher number of hemiarch resection in BACP group (p=0.10). Intraoperative variables are listed in Table 2.

Overall in-hospital mortality was 17.9% and no differences were found between groups (UACP 20% *vs.* BACP 15.8%, p=0.56). Four patients died for cardiovascular causes (pulmonary arterial embolism, n=1, cardiogenic shock, n=1, acute right heart failure n=1, aortic rupture, n=1), 8 patients for primitive respiratory failure, 4 for multiple organ failure, 2 for diffuse bleeding, 1 for neurological damage, another one for septic shock. PNI occurred in 15 patients (12.3%) and the differences between the two groups of study did not reach a statistical significance (UACP 10.9% *vs.* BACP 15.8%, p=0.45) (Table 3).

| | UACP n=55 | BACP n=57 | p-value |
|---|---|---|---|
| 30-day mortality, n (%) | 11 (20.0) | 9 (15.8) | 0.56 |
| Permanent neurologic injury, n (%) | 6 (10.9) | 9 (15.8) | 0.45 |
| Renal failure requiring CVVHF, n (%) | 9 (16.4) | 7 (12.3) | 0.54 |
| Respiratory failure, n (%) | 9 (16.4) | 12 (21.0) | 0.53 |
| Re-exploration for bleeding, n (%) | 11 (20.0) | 15 (26.3) | 0.43 |
| ICU stay (days), mean ± SD | 6.2 ± 6.1 | 9.6 ± 16.6 | 0.15 |
| Postoperative stay (days), mean ± SD | 13.9 ± 9.9 | 17.0 ± 15.8 | 0.22 |

**Table 3:** Early postoperative outcomes. ICU: Intensive Operative Unit; CVVHF: Continuous Veno-Venous Haemofiltration.

At univariate analysis risk factor for PNI in the whole cohort were a circulatory arrest time, expressed as categorical variable, greater than 30 min (p=0.09) and a concomitant endovascular repair of the descending aorta (p=0.07). Nevertheless, when including in multivariable model, they lost the significance (Table 4).

For in-hospital mortality the complete aortic arch replacement (p=0.06), aortic root sparing (p=0.03), age >75 years (0.05), respiratory failure including the need for reintubation or prolonged ventilation (>3 days) (p=0.003), acute kidney injury requiring continuous veno-venous haemofiltration (p=0.001) reached the statistical significance at the univariate analysis and were included in multivariable model. Independent predictors of in-hospital mortality were the complete aortic arch replacement (OR 4.7, 95% CI: 1.2-18.2), age >75 years (OR 3.8, 95% CI: 1.1-13.5), acute kidney injury requiring continuous veno-venous haemofiltration (OR 4.7, 95% CI: 1.2-18.5) and respiratory failure (OR 9.9, 95% CI: 2.0-49.9) (Table 4).

| Variable | Univariate | | Multivariate | |
|---|---|---|---|---|
| | P-value | OR | CI 95% | P-value |
| Permanent neurologic injury | | | | |
| Circulatory arrest time >30 min. | 0.09 | 2.2 | 0.6-7.7 | 0.23 |
| Endovascular descending aorta repair | 0.07 | 3.3 | 0.7-16.6 | 0.15 |
| In-hospital mortality | | | | |
| Age>75 years | 0.05 | 3.8 | 1.1-13.5 | 0.04 |
| Complete aortic arch replacement | 0.06 | 4.7 | 1.2-18.2 | 0.03 |
| Aortic root sparing | 0.03 | 0.6 | 0.1-6.2 | 0.7 |
| AKI requiring CVVHF | 0.001 | 4.7 | 1.2-18.5 | 0.03 |
| Respiratory failure | 0.003 | 9.9 | 2.0-49.9 | 0.005 |

**Table 4:** Permanent neurologic injury and in-hospital mortality risk factors analysis. AKI: Acute Kidney Injury; CVVHF: Continuous Veno-venous Haemofiltration.

## Discussion

In order to reduce neurological complications and to improve safety and efficacy of cerebral protection during aortic surgery, several techniques of cerebral protection have been developed. However, the optimal modality for cerebral protection is still debated.

Historically, open aortic surgery was performed in deep HCA, introduced by Griepp et al. in 1975 [14]. This strategy is based on the depression of cerebral and systemic metabolism through the deep hypothermia. Nevertheless, there are several limitations with this approach, including a limited safe time of circulatory arrest, an increased incidence of postoperative neurological complications after circulatory arrests longer than 25 min, a prolonged time of CPB, clotting disturbances and postoperative pulmonary, renal, cardiac and endothelial dysfunction [15].

To avoid these severe complications, alternative techniques, such as retrograde cerebral perfusion and antegrade selective cerebral perfusion (ASCP), with various levels of systemic hypothermia, have been proposed. These techniques improve the safety of open aortic procedures by decreasing the postoperative morbidity and mortality [9]. However, retrograde perfusion through the superior vena cava failed to demonstrate sufficient cerebral blood flow [16]. Selective antegrade perfusion offers a more physiologic method of cerebral perfusion and appears to be the most promising tool for reducing morbidity and mortality in open aortic arch surgery [17].

Currently, moderate hypothermia (22°C to 26°C) associated with selective antegrade cerebral perfusion has been reported to be the preferred method of cerebral protection among European centers, administered with a perfusion flow of 10 to 15 ml/kg/min to achieve a perfusion pressure of about 60 mmHg [18]. Despite this wide consensus about antegrade selective cerebral perfusion, BACP of supra-aortic vessels is not always warranted, with almost 40% of those European centers performing UACP [18].

Our current approach for patients who underwent emergency aortic surgery is selective ACP (UACP or BACP) and mild-to-moderate hypothermia (26°C).

The issue of UACP versus BACP has been examined in aortic arch surgery but few reports focus exclusively upon acute proximal aortic dissection. In a similar report concerning patients who underwent partial and total aortic arch repair, Zierer and colleagues demonstrated that UACP offers as much brain and visceral organ protection as BACP and might be advantageous, as it avoids manipulation of the aortic arch vessels [19].

In a recent meta-analysis, BACP allowed for longer circulatory arrest times. In fact, once cerebral perfusion exceeded 40 to 50 min, BACP was documented to be safer [20].

In theory, BACP should be better than UACP providing a superior cerebral protection. Actually, in our series, we did not observe any significant statistical and clinical differences between the two strategies. Because of the existence of the circle of Willis, hypothetically the absence of one of the three communicating arteries in the circle of Willis should not cause hypoperfusion. The right axillary artery could perfuse the entire brain through the vertebral artery, the basilar artery, and the internal carotid artery [21]. Left-side cerebral hypo-perfusion would occur only in the absence of both the anterior and the posterior communicating arteries; however, this situation is very rare and it has not been reported in the relevant literature.

Experienced groups [22] recommend elective preoperative evaluation of the cerebral circulation because an incomplete circle of Willis can occur in 6% to 17% of cases [23,24]. We do not routinely image the circle of Willis as others have suggested; however, we routinely use NIRS intraoperatively in order to shift to BACP if necessary. In particular, BACP was always required when there was asymmetry of the INVOS value between the two hemispheres, and the INVOS value dropped below 20-25% of the baseline value.

Our overall rate of PNI was 12.3%, and no differences were found between the two techniques, as reported by also others [25,26]. Furthermore, intraoperative variables such as CPB, aortic cross clamp and circulatory arrest times were similar between the groups.

We only recorded a statistical significance about the arterial access for CBP that was mainly *via* femoral artery in BACP group (67.5%, p=0.01) and right axillary artery in UACP group (57.3%, p=0.03).

The choice of the optimal arterial cannulation site is also a subject of debate. Femoral cannulation has been identified as an independent predictor for in-hospital mortality and worse neurologic outcome, probably because of the risk of retrograde cerebral embolization [27,28].

In the last years we routinely used right axillary artery cannulation both for CPB and UACP or BACP by means of a side-biting clamping of the top of the aortic arch [12,13]. The main advantage of this technique is that the axillary artery tends to have less atherosclerosis and is less likely to have dissection [28,29].

The advantage of axillary cannulation and antegrade perfusion during CPB compared with femoral cannulation with retrograde flow on in-hospital mortality and early neurologic outcome after elective aortic surgery for atherosclerotic aneurysms has been previously suggested [30-32]. However, its advantage on outcome after emergency repair for AAAD remains controversial, and conclusive data proving superiority of antegrade perfusion in these cases are not yet available [29,31,33].

No independent predictors of PNI were identified in our series. A circulatory arrest time, expressed as categorical variable, greater than 30 min and a concomitant endovascular repair of the descending aorta, lost their significance at multivariate analysis (Table 4).

Our in-hospital mortality rate of 17.9% is comparable with that of others [25-27], and we observed no differences in survival probability between the two groups.

Lu and colleagues demonstrated the non-inferiority of UACP in comparison with BACP in patients undergoing arch reconstruction for aortic dissection [34]. In contrast, Wiedemann and coworkers showed that the BACP group had better 30-day survival (19% *vs.* 5%; p=0.059) [25].

In 2007, the IRAD investigators proposed a risk model for early mortality, in which age >70 years, prior aortic valve replacement, preoperative systemic hypotension, shock or tamponade, migrating chest pain, any pulse deficit, intraoperative hypotension, right ventricular dysfunction and coronary artery bypass graft were identified as risk factors for mortality. On the contrary, the partial arch replacement was associated with lower mortality [35].

In our entire series, the multivariate regression analysis showed that complete aortic arch replacement, age >75 years, acute kidney injury requiring replacement therapy, and respiratory failure were independent risk factors for operative mortality. On the other hand, the proximal extension of the surgical correction of the dissected aorta did not affect early results. Therefore, if the root is involved, either a valve-sparing operation or a Bentall procedure can be performed with a relative safeness [36].

Even the role of patient's age is somewhat controversial. In one of the earlier papers on this topic, Neri and colleagues analyzed surgical results in octogenarians, and they concluded that a found 30-day mortality of 83% and an intraoperative mortality of 33% were excessively high to justify a surgical repair in this subgroup of patients [37]. In 2002, Mehta and coworkers analyzed data from the IRAD, stratifying patients by age with a cutoff of 70 years: postoperative complications were similar in the two groups; among patients treated surgically, in-hospital mortality was higher in the elderly cohort (37.5% *vs.* 23%) but still lower than medically managed patients of corresponding age [38]. In 2010, Trimarchi et al. reviewed the IRAD and, analyzing in-hospital mortality of medically versus surgically managed patients, concluded that surgery continued to be recommended for patients aged 70-80 years and beneficial for octogenarians [4]. Similar conclusions were found by Rylski et al. collecting data from the German Registry for Acute Aortic Dissection Type A registry [39]. Our experience showed that older patients (age >75 years) had a four-fold increased risk of in-hospital mortality, and the indication to surgery should be cautiously evaluated case by case.

This is a retrospective, observational, nonrandomized study and several limitations should be kept in consideration: first, unrecognized risk factors might affect clinical outcomes. Secondly, the preoperative presence of malperfusion was not evaluated during the study, although it can be assumed that the incidence of malperfusion was homogeneously distributed between the two groups of patients.

Furthermore, this study represents a single-center experience focused on the difference between UACP and BACP, and the sample is relatively small, thus underestimating the statistical power of the analysis, although it reflects quite a large real world practice.

In conclusion, our study on cerebral protection in AAAD showed there is no evidence that BACP is superior to UACP combined with HCA for emergency aortic arch surgery in preventing early PNI and in-hospital mortality. BACP can be achieved with security also *via* right axillary cannulation alone, with no increased of PNI and in-hospital mortality.

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