Neurologic and cognitive outcomes after aortic arch operation with hypothermic circulatory arrest

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Neurological and cognitive outcome after aortic arch surgery with hypothermic circulatory arrest.

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Abstract

Objective

Neurological damage is still a frequent cause of mortality, morbidity and long-lasting disability in patients undergoing aortic arch surgery with hypothermic circulatory arrest. The aim of this analysis was to evaluate short and long-term outcome in neurological and cognitive function in this group of high risk patients.

Methods

Three hundred and thirty-tree patients undergoing aortic arch surgery between February 2004 and June 2010 were retrospectively reviewed. Cerebral protection was obtained with deep hypothermic circulatory arrest in 220 patients (66%) or with moderate hypothermic circulatory arrest in 113 cases (34%). Straight deep hypothermic circulatory arrest was adopted in 35 cases (11%), while the association with antegrade cerebral perfusion was adopted in 271 cases (81%) and with retrograde cerebral perfusion in 27 cases (8%). Seventy-eight patients were enrolled in a case control prospective study (mean follow-up time = 42 months) and underwent neuropsychological evaluations; data were compared with those of a matched-control group of hypertensive patients without history of cardiac surgery procedures.

Results

Forty-one out of 333 patients experienced permanent neurological dysfunction (12%), and 83 experienced temporary neurological dysfunctions (25%). Acute aortic dissection and deep hypothermic circulatory arrest were significant predictors of mortality and permanent neurological dysfunction. Acute aortic dissection and hypothermic circulatory arrest duration >30 min were significant predictors of temporary neurological dysfunction, while antegrade cerebral perfusion was protective on mortality.

Neuropsychological evaluations showed no significant differences between subgroups of surgical patients, but when compared to control group they was found to perform worse in verbal short and long-term memory (p = .035), , and to be more alexithymic (p = .054) and with a lesser quality of life (p = .054).

Conclusions

Moderate hypothermic circulatory arrest with antegrade cerebral perfusion gave the best result in the early outcome in terms of mortality. Comparative analysis demonstrated that surgical patients performed worse in the long term incognitive and psychological functioning.

Objective

Aortic arch surgery with hypothermic circulatory arrest (HCA) represents, to date, a challenging task and high-risk cardiovascular procedure. Particularly, neurological damage is still a frequent cause of perioperative mortality and morbidity after this kind of operation. The incidence of permanent neurological dysfunction (PND), as reported by various studies and registries, is between 2% and 5% for elective cases and 9% to 16% for urgent and emergency cases.[1]

Moreover it is known that neurologic damage can also occur as temporary neurological dysfunction (TND), which is a functional expression of fine and presumably transient brain injury, theoretically capable of determining long-term deficits of cognitive and intellectual functions and alterations of the neuropsychological profile of the patients.[2]

Until now there has been no general agreement on the safest technique to adopt to reach the best cerebral protection. Concerns remain about the temperature to reach during circulatory arrest, the employment of selective cerebral perfusion (SCP) and the site of arterial cannulation.

The aim of this report is to evaluate postoperative short term outcome in patients undergoing elective and non-elective cardiac operations with HCA and cerebral perfusion through a retrospective analysis; and to assess long-term deficits in neurological and cognitive function with a case control prospective study.

Materials and methods

Patients

A total of 333 consecutive patients, who underwent aortic arch surgery with HCA at the University Hospital of Turin, from February 2004 to June 2010, were retrospectively reviewed. The mean age was 64 years (range 21-80) and 90 patients (27%) were females. Table 1 shows overall preoperative characteristics, intraoperative data and early outcome.

One hundred and twenty four patients (37%) with chronic lesions underwent elective surgery and 209 patients (63%) with acute aortic syndrome underwent emergency surgery; the reason for emergency surgery was acute type A aortic dissection in 190 cases (91%), intra-mural hematoma in 12 cases (6%), and 7 patients had miscellaneous aetiologies (3%).

Definitions

According to a recent consensus of thoracic aortic experts from all over the world HCA was considered deep between 14.1 and 20° Celsius, moderate between 20.1-28° Celsius and mild between 28.1-34.0 degrees Celsius.[3,4]

The short-term outcome variables were early mortality (EM), and neurological event (NE), divided in PND and TND. EM was defined as death within the hospital or within 30-day from the surgical procedure. PND was defined as clinical signs persisting at the time of discharge from the hospital and/or in the presence of localized ischemic infarcts detectable by conventional neuroimaging techniques. TND was defined as temporary clinical signs by means of confusion, agitation, delirium, prolonged obtundation or transient stroke with negative cranial computed topographic (CT) scan and complete resolution before discharge.[2]

The long-term outcome variables were the occurrence of neurological or cognitive deficits in the follow-up assessed by neurological objective examination and neuropsychological testing.

Surgical technique and cerebral protection

All patients were operated on through a median sternotomy incision. Usual conventional hemodynamic monitoring and endotracheal intubation were performed. All patients received a standard anaesthetic and neurological monitoring. All patients were ventilated with a standard protocol (continuous mandatory ventilation, pCO_2 35-45 mmHg). The anaesthesia and the curarization for all patients were provided through continuous intravenous drugs. The induction was provided by Midazolam, Fentanyl or Sufentanil, and Cisatracurium. The maintenance was provided by Propofol, Cisatracurium, and Sufentanil.

Hemodynamic monitoring included right and left radial arterial pressure lines as well as central vein pressure monitoring. The bispectral index was used to monitor narcosis level. The near infrared spectroscopy (NIRS) was placed before the anaesthetic induction to monitor brain perfusion. NIRS values decrease till 20% of the basal ones were tolerated.

Transesophageal echocardiography was routinely used for confirmation of the diagnosis and for assessment of the aortic valve function and morphology. A temperature probe was placed for nasopharyngeal temperature monitoring.

After systemic heparinization (300 IU/kg), the arterial inflow was obtained through the femoral artery in 143 patients (43%) and through the axillary artery in 175 (52%). Only in 15 elective patients (5%) was the central cannula used. Venous drainage was obtained through a 2-staged venous cannula in the right atrium. The left ventricle was vented through the right superior pulmonary vein. Cardiopulmonary bypass (CPB) was started, and the heart was arrested with intermittent selective antegrade CPB isothermic cardioplegia.

Cerebral protection was obtained by means of deep HCA in 220 patients (66%), and by means of moderate HCA in 113 patients (34%). Straight deep HCA was adopted in 35 cases (11%), while HCA and antegrade cerebral perfusion (ACP) was adopted in 271 cases (81%), and HCA and retrograde cerebral perfusion (RCP) by directly cannulating the superior vena cava was adopted in 27 patients (8%). In both cases of ACP or RCP the system was connected to the cardioplegia line, which was used as arterial inflow.

ACP was achieved by selectively cannulating the epiaortic vessels (142 patients, 52%) or by using the right axillary way (129 patients, 48%). Every time the right axillary artery was cannulated, the epiaortic vessels were snared and the unilateral ACP was established using the axillary route; in the case of bilateral perfusion a selective cannulation of the left internal carotid artery was added.

Selective cerebral flow rate was maintained at approximately at 10 ml/kg/min. Mean arterial blood pressure was maintained between 40 and 70 mmHg.

During HCA, the patients head was packed in ice, to prevent brain rewarming.

All patients underwent standard neurologic examination focused on PND and TND after awakening from anesthesia and every day of their hospital stay. Each patient with a recognized neurologic deficit underwent specialist neurologic assessment and cranial CT scan.

Study design

All patients who underwent aortic arch surgery with HCA and who were discharged home alive during this period were potentially considered eligible to be enrolled in the case control prospective study. The inclusion criteria were: i) age≥18 years and ≤80 years; ii) ability to perform the neuropsychological test, no severe language or motor deficits; iii) normal or corrected to normal vision. The exclusion criteria were: i) age <18 years or >80 years; ii) neurocognitive deficit before surgery; iii) neurocognitive status not assessable before surgery; iv) illiteracy; v) drug or alcohol abuse vi) neurological diseases or psychiatric diseases unrelated to perioperative events.

Of 248 patients without neurocognitive deficit before surgery, 36 died (15%) and 17 (7%) were lost at follow-up (e.g. could not be contacted); of 195 contacted patients, 85 accepted the be enrolled in the study (44%), but 7 were excluded according to the above criteria.

The subgroup of 78 patients, that accepted to undergo to neurological and neuropsychological assessment, was evaluated between November 2011 and April 2012. The mean age was 66 years (range 38-80), 11 patients (14%) were females and the mean follow-up time was of 42 months (range 8-80 months) (Table 2). All patients signed an informed consent in accordance with the Helsinki declaration.

No differences were observed in terms of pre-operative and intra-operative characteristics and early outcome between this subgroup of patients and those discharged home alive who did not subscribe test (see Table 1 and 2).

An expert neurologist assessed standard neurological examination evaluating sensory, motor, locomotion, cranial nerve, language and reflexes deficits; the assessment also included a complete clinical and demographic anamnesis.

The order of administration was the same for each patient and was chosen taking into account the execution time of each test and the cognitive domain concerned. The battery included neuropsychological tests to assess cognitive impairment, short- and long-term verbal and visual memory, working memory, processing-attention, linguistic fluency and executive functions and self-administered scales to assess depression, anxiety, alexithymia, distress, sleep quality, apathy and quality of life for a total of 11 cognitive tests and 6 psychological questionnaires. The maximum duration for the assessment was an hour and a half. The patient along with a qualified psychologist filled out the interview-administered questionnaires after the administration of the neuropsychological protocol. A detailed description of tests and questionnaires can be found in the Supplementary Materials.

A comparative analysis was performed on a matched-control group of 27 hypertensive patients with the same characteristics, risk factors and comorbidities of the study group population, but without cardiac surgical procedures (Table 2). The control group was randomly selected from the outpatients clinic of the Division of Internal Medicine, Hypertension Unit, of our Hospital.

Statistical analyses

All statistical analyses were performed with IBM SPSS Statistics for Windows, Version 20.0.0 (Armonk, NY: IBM Corp.).

A descriptive and main statistical analysis was performed on the overall cohort of 333 patients. Continuous variable data was described with mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate on statistical distribution; categorical variable data was represented with frequency and percentage. In univariate analysis comparison for outcome (EM, TND, PND, NE) we used a t-test or Mann-Whitney U for continuous variables and a Chi-square or Fisher's exact test for categorical variables, using intra- and pre-operative variables to split the sample into subgroups (aortic dissection, HCA >30 min, Deep HCA, cannulation and perfusion setup). We also performed Receiver Operating Characteristic curve (ROC) analysis for temperature and duration of HCA. All factors with a significance level $p < 0.05$ in univariate analysis were entered into a logistic regression model multivariable. The results were expressed with Odd Ratio (OR) and a confidence interval of 95% (CI 95%). All statistical tests were two-sided and P values <.05 were considered statistically significant.

A second descriptive analysis was performed on the study follow-up group of 78 patients.We used the same comparison tests of the first analysis to explore the effects of pre-, intra- and post-operative variables on neurocognitive outcome (neurological and neuropsychological scores) looking to the possible effects of aortic dissection, HCA >30 min, Deep HCA and presence of TND.

Finally a comparison analysis was performed between the follow-up group and the control group for all the tests and questionnaires.

Due to the large number of variables taken into account, we corrected the *p* values using Finners' step down correction for controlling the Family Wise Error rate (FWE correction) for cognitive, and psychological scores.[5,6] We also compared the frequency of deficits between groups using Italian normative data when possible. We used Pearson's correlation to evaluate the relationships between scores and clinical and demographic variables.

Results

Forty-one patients (12%) experienced PND, and 83 patients (25 %) experienced TND. Overall EM was 22% (73/333). In the subgroup of patients with diagnosis of acute aortic syndrome TND were 32% (61/190 cases), PND were 18% (34/190 cases) and EM was 26% (50/190 cases).

ROC curve analysis on HCA duration and temperature during circulatory arrest showed no significant results for NE, TND and PND; only temperature was significant for EM with a cut-off < 19.4° C ($p < 0.001$, AUC = 0.65, sensitivity 85%, specificity 45%).

Univariate analysis showed that acute aortic dissection was associated with higher EM (P=.03), NE (P< .01), TND (P<.01) and PND (P<.01). Deep HCA was associated with increased EM (P<.01), PND (P=.03) and NE (P=.03). HCA duration >30 min was related with TND (P=.02) and ACP was associated with a reduction of EM (P=.02) (fig 1-2).

Logistic regression showed that acute aortic dissection and deep HCA were significant risk factors for EM, PND and NE. Acute aortic dissection and HCA duration >30 min were significant predictors of TND, while ACP was protective on EM (Figures 1, 2).

Seventy-eight patients underwent neurological and neuropsychological evaluations at the time of follow-up. Fourty-five out of 78 patients had had diagnosis of acute aortic syndrome and underwent emergent procedure. Cerebral protection was obtained by means of deep HCA in 45 patients (58%), and by means of moderate HCA in 33 patients (42%). Antegrade cerebral perfusion was adopted in 71 cases (91%), and RCP in 6 cases (8%). In all the comparison between subgroups of the follow-up patients they were matched for demographic and clinical variable of interest (Supplementary Table S1). No significant neurocognitive differences were found between elective surgery patients versus urgent surgery patients (Table 3, Supplementary Table S2-6), between patients who developed post-operative TND versus who did not (Table 3, Supplementary Table S7-11) and between patients who underwent deep versus moderate HCA (Table 3, Supplementary Table S12-16).

Moreover no significant neurological differences were reported between the study group and the matched control group (Table 4, Supplementary Table S17), but the surgical group was found to perform worse in verbal short (12.0 ± 5.5, 15.7 ± 4.7, p = .035) and long-term memory (11.1 ± 4.6, 14.2 ± 4.5, p = .035), and to be more alexithymic (61 ± 14, 51 ± 12, p = .054) and with a lesser quality of life in physical functioning (74 ± 25, 86 ± 16, p = .054) (Table 3, Supplementary Table S18-21). No clinical or surgical data linked with the above deficits (Supplementary Table S22).

Comparing the numbers of patients that presented clinical significant neurocognitive deficits between subgroups of the follow-up study group, only aortic dissection were less frequently distressed (56% vs. 80%), but we found no other differences (Table 4). Looking at the same comparison between the follow-up study group and the control group (Table 4) we found more frequent deficits in patients that underwent to surgery in short (24% vs. 15%, p = .029) and long term memory (21% vs. 7%, p = .031), alexithymia (48% vs. 31%, p = .051) and physical functioning quality of life (27% vs. 4%, p = .018).

Discussion

The aim of this retrospective analysis was to evaluate early and long-term neurological events in patients undergoing cardiac operations with HCA. Particularly we focused on different intra-operative techniques of cerebral protection potentially affecting the incidence of PND, TND and long-lasting neurocognitive deficits**.** Despite the results of aortic arch surgery having steadily improved in recent years, concerns still remain about the safest technique to adopt to reach the finest cerebral protection. The most recognized technique is hypothermia, but the grade of cooling, the safe duration of HCA, and the route and temperature of perfusate for selective cerebral perfusion are still fields of debate.

We reported an overall EM of 22% and PND were observed in 12% of the patients. These data are at a higher level when compared with other reports and can be explained bearing in mind that our population includes a high rate of emergency procedures (63%) and that the technique of brain protection was not homogeneous. In the subgroup of patients with diagnosis of aortic dissection, EM was 26%, and PND were 18%, in line with other report in literature.[2,7-11] The finding that aortic dissection was a risk factor for both mortality, PND and NE was not unexpected, and it is in accord with the observations of others.[8,9,12-14] An important result of this study was that in the follow-up neurocognitive analysis did not show worse postoperative impairment in cognitive, psychological and neurological functions in the case of dissection compared to non-dissection.

Many surgeons still insist on a deep-cold hypothermia of 10°–13°C to avoid neurologic damage.[15] Conversely, other groups have supported a higher temperature of hypothermia (25°–28°C).[9,16] Minatoya et al., in 229 patients with HCA and SCP during aortic arch replacement, compared 81 patients cooled to 20°C, 81 cooled to 25°C, and 67 cooled to 28°C and claimed that the rate of postoperative neurologic events did not increase with use of moderate HCA.[17] Similarly, Kamiya and colleagues, in a propensity-matched comparison between HCA at 20.0-24.9°C and HCA at 25-28°C did not find any significant differences in mortality and morbidity; they only observed a trend towards a lower post-operative inflammatory response and reduced re-exploration for bleeding in the second group.[18] Strauch et al. has asserted that brain oxygen consumption drops down to 50% of baseline value with moderate hypothermia (28°C) and that further cooling does not decrease brain oxygen consumption effectively.[19]

Moreover our series showed that deep HCA was a significant predictor of PND, NE and EM and that it did not seem to be a protective factor in the follow-up on neurocognitive impairment.

Previous studies have consistently demonstrated the role of ACP in extending the safe duration of HCA and reducing the risk of NE.[3,20] in a recent meta-analysis by Tian et al., that compared deep HCA only with moderate HCA and ACP, PNDs were significantly higher in the first group (12.8% vs. 7.3%, OR 1.80, P<.001). No differences were observed in mortality, TND, renal failure, bleeding and re-operation between the two methods.[21] Also Bakhtiary et al., observed a low rate of PND (4.2%) under mild hypothermic conditions combined with ACP.[11] In the present study, we observed that ACP was protective for early mortality and that the stroke incidence was not related to unilateral or bilateral perfusion. This is in line with other reports.[13,21]

Literature data shows that circulatory arrest time can also affect early and late outcome. McCullough et al. demonstrated that the predicted safe duration of HCA at 15°C is only 29 minutes and at 10°C about 40 minutes.[22] In this report we found that cerebral arrest duration >30 minutes was associated with TND. This is in line with what was reported by other authors. [2,23-25] Subgroup neurocognitive analysis on 78 patients did not show prolonged postoperative impairment in cognitive, psychological and neurological function regarding diagnosis of aortic dissection, temperature of HCA and occurrence of transient neurological deficit. On the other hand, comparative analysis with the control group clearly demonstrated that surgical patients performed worse in short and long term verbal memory, alexithymia and physical functioning. Differences, even if less statistically significant, were observed in semantic fluency and physical limitation.

The assessment of neurologic outcome in adult patients undergoing HCA is, to date, prevalent in reporting incidence of postoperative stroke and TND. Clinical studies on late neuropsychological sequelae are limited and controversial.

Welz et al., assessed late neuropsychological outcome after deep HCA in 23 patients who had undergone deep HCA and compared those with 10 healthy subjects. The patient group performed worst on all tests and the level of impairment in sustained attention was correlated with duration of deep HCA.[26] Reich et al. compared patients undergoing routine cardiac surgery with patients who had surgery of the thoracic aorta with periods of deep HCA and showed that prolonged deep HCA (more than 25 minutes) and advanced age were significant predictors of poor performance at 6 weeks for both memory and fine motor domains.[27] Ergin et al. revealed a persistent loss of cognitive function and deterioration in postoperative cognitive scoring-testing lasting more than 6 weeks in patients who underwent aortic arch surgery by using HCA for more than 25 min at 10°C. Moreover they found a significant correlation between the TND clinical severity and cognitive impairment suggesting that TND may not be entirely a transient phenomenon, but may be a marker for long-lasting cognitive deficits.[2] While these results are compatible with ours, no follow-up data of more than 3 years has so far been collect. From our data it emerged that some kind of brain damage in spite of adequate protection remains in HCA procedure and that it goes beyond a clear cause (hypoxic, cold, embolic damage) as no evident risk factor emerged in subgroup analysis.

The main limitations of this study are that it is a single-center study carried out retrospectively, the small numbers in subgroups,and the long study period. In addition, a non negligible portion of patients (22%) was lost in follow-up.

In conclusion**,** in our experience moderate HCA with axillary ACP gives the best possible result in the short term outcome, but it is not protective enough in the long term (compared with the population that has not suffered circulatory arrest). Other roads should be taken to protect patients from long-lasting cognitive impairment.

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Table 1: Overall preoperative characteristics, intraoperative data and early outcomes

Variable (n=333)	Value
Age, y (mean, SD)	64 ± 12
Female (n, %)	90 (27)
Hypertension (n, %)	151 (45)
BPCO (n, %)	18 (5)
Peripheral vasculopaty (n, %)	21 (6)
Previous cardiac surgery (n, %)	50 (15)
Emergent surgery (n, %)	209 (63)
Preoperative neurological deficit (n, %)	51 (15)
Preoperative neurological deficit not evaluable (n, %)	37 (11)
Type of aortic disease (n, %)	
Acute type A aortic dissection	190 (57)
Degenerative aneurysm ± aortic regurgitation	81 (24)
Intra-mural hematoma	12 (4)
Other	50 (15)
Surgical procedures (n, %)	
Ascending aorta + hemiarch replacement	169 (51)
Ascending aorta + hemiarch replacement + aortic valve surgery	80 (24)
Total arch replacement	40 (12)
Total arch replacement + Elephant Trunk	21 (6)
Other	23 (7)
Total surgery time, min (mean, SD)	368 ± 165
Cardiopulmonary bypass time, min (mean, SD)	193 ± 70
Crossclamp time, min (mean, SD)	105 ± 45
Arterial cannulation (n, %)	
Central	15 (5)
Femoral	143 (43)
Axillary	175 (52)
Hypothermic circulatory arrest time, min (mean, SD)	39 ± 24
Hypothermic circulatory arrest temperature (n, %)	
Deep hypothermic circulatory arrest	220 (66)
Moderate hypothermic circulatory arrest	113 (34)
Cooling time, min (mean, SD)	55 ± 26
Rewarming time, min (mean, SD)	66 ± 23
Selective cerebral perfusion (n, %)	
Antegrade	271 (81)
Retrograde	27 (8)
No perfusion	35 (11)
Early Mortality (n, %)	73 (22)
Neurological Event (n, %)	124 (37)
Permanent Neurological Dysfunction (n, %)	41 (12)
Transitory Neurological Dysfunction (n, %)	83 (25)
Reoperation for bleeding (n, %)	39 (12)
Renal dysfunction	18 (5)
Pulmonary complication	58 (17)

Table 2: Demographic data and risk factors

Data / Groups	Study group (n=78)	Control group (n=27)	*p**
Age, y (mean, SD)	66 ± 10	64 ± 11	0.47
Male gender, n (%)	67 (86)	23 (85)	1.00
BMI, kg/m^2 (mean, SD)	27 ± 4	26 ± 3	0.47
Right-handed, n (%)	78 (100)	27 (100)	1.00
Education, y (mean, SD)	10 ± 4	11 ± 4	0.13
Diabetes, n (%)	8 (10)	4 (15%)	0.48
Hypertension, n (%)	78 (100)	27 (100)	1.00
SBP, mmHg (mean, SD)	133 (16)	135 (14)	0.62
Cerebrovascular disease, n (%)	14 (18)	3 (11)	0.55
Atrial Fibrillation, n (%)	6 (8)	0 (-)	0.33
Smoker no/past/yes, n (%)	4/52/22 (5/67/28)	4/16/7 (15/59/26)	0.34
Cardiological disease familiarity, n (%)	41 (52)	17 (63)	0.37

SBP: systolic blood pressure. Data indicated mean or median, in parenthesis SD or IQR or percent. BMI = Body Mass Index. *p values for t-test or Mann-Whitney U for continuous variables and a Chi-square or Fisher's exact test for categorical variables.

Table 3: Neurocognitive outcomes

Variables	Neurologic	Cognitive	Cognitive PAT	Psychological	Psychological PAT
Ao dissection, y<n	NS	NS	NS	Distress, Vitality	NS
Post-op TND, y>n	NS	NS	NS	Physical limitation, Bodily pain	NS
Deep versus moderate HCA	NS	NS	NS	NS	NS
Study group vs control group	NS	**Verbal memory short-term and long-term**, working memory, semantic fluency	Verbal memory short-term and long-term	**Alexithymia, Physical Functioning,** Physical Limitation	Alexithymia, Physical Functioning

Scores in neurologic, neuropsychologic and psychological scales that differed between groups. PAT = number of pathological subjects significantly different between groups. NS = Not Significant, Ao = aortic, Post-op = Post-operative, TND = Transitory Neurological Dysfunction.

In **bold** results significant after multiple comparisons correction.

Figure 1: Analyses of the association between pre-operative and intra-operative risk factors and early mortality.

Subgroup	Univariate analysis *No. at risk*		*p*	Logistic regression *Odds Ratio*	*(95% CI)*	*p*
Aortic dissection y / n	26%	16%	**0.03**		2.37 (1.12-5.02)	**0.02**
HCA > 30 min / < 30 min	25%	20%	0.29			
Deep HCA / Moderate HCA	28%	9%	**<0.001**		3.98 (1.59-9.93)	**<0.001**
Unilateral / Bilateral Perfusion	27%	16%	0.07			
Other Perfusion / ACP	33%	18%	**0.02**		0.33 (0.15-0.73)	**0.01**
Femoral / Axillary Cannulation	19%	15%	0.50			

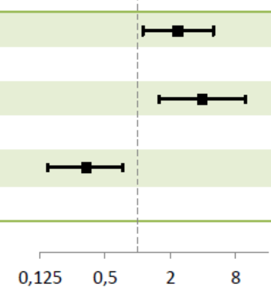

Figure 2: Analyses of the association between pre-operative and intra-operative risk factors and overall neurological events (NE), permanent neurological dysfunction (PND), and temporary neurological dysfunction (TND).

Subgroup	Univariate analysis *No. at risk*		*p*	Logistic regression *Odds Ratio (95% CI)*	*p*
	NE				
Aortic dissection y / n	49%	19%	**<0.001**	4.12 (2.30-7.38)	**<0.001**
HCA > 30 min / < 30 min	42%	34%	0.25		
Deep HCA / Moderate HCA	43%	29%	**0.03**	1.77 (1.01-3.14)	**0.05**
Unilateral / Bilateral Perfusion	32%	41%	0.22		
Other Perfusion / ACP	36%	37%	0.86		
Femoral / Axillary Cannulation	36%	39%	0.89		
	PND				
Aortic dissection y / n	17%	5%	**<0.001**	4.16 (1.59-11.22)	**<0.001**
HCA > 30 min / < 30 min	9%	15%	0.19		
Deep HCA / Moderate HCA	16%	7%	**0.03**	2.53 (1.01-6.46)	**0.05**
Unilateral / Bilateral Perfusion	7%	15%	0.12		
Other Perfusion / ACP	5%	13%	0.13		
Femoral / Axillary Cannulation	14%	11%	0.55		
	TND				
Aortic dissection y / n	32%	14%	**<0.001**	2.98 (1.56-5.68)	**<0.001**
HCA > 30 min / < 30 min	33%	19%	**0.02**	2.12 (1.19-3.75)	**0.01**
Deep HCA / Moderate HCA	27%	22%	0.46		
Unilateral / Bilateral Perfusion	25%	26%	0.87		
Other Perfusion / ACP	31%	24%	0.34		
Femoral / Axillary Cannulation	22%	28%	0.45