Cerebral perfusion issues in type A aortic dissection

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Abstract: Stroke events are very common in acute type A aortic dissection. Cerebral malperfusion could manifest at presentation due to prolonged arch vessels hypoperfusion or develop after surgery for inadequate cerebral protection during arch repair. To reduce this detrimental complication there are several adjuncts that can be adopted for cerebral protection such as direct antegrade or retrograde cerebral perfusion (RCP) and use period of deep to moderate hypothermic circulatory arrest time; however, they are often insufficient as preoperative malperfusion already caused irreversible ischemic damages. The aim of the current review article is to analyze the principal series reporting on neurological injuries during type A aortic dissection to focus on the outcomes according to the type of surgical management and identify possible predictors to better manage this complication.

Keywords: Type A aortic dissection; brain protection; cerebral perfusion; antegrade selective cerebral perfusion (ASCP); hypothermic circulatory arrest

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Introduction

There is no doubt that adequate cerebral protection during any kind of arch surgery plays a key role in achieving successful outcomes. Aortic arch reconstruction in type A acute aortic dissection (TAAAD) always requires to protect the brain from ischaemic and embolic injury, to ensure patency of the brachiocephalic vessels with reduced trauma to these friable vessels, and to restore the blood flow in to the true lumen performing a durable distal anastomosis.

Currently, it has been largely demonstrated that optimizing cerebral protection with hypothermia and adjunctive cerebral perfusion allows for safe, extended periods of circulatory arrest and open arch reconstruction (1-3).

However, neurological injuries still represent a relevant issue in aortic dissection because the frequency of both preoperative and postoperative cerebral events is high and negatively impact the prognosis of these patients. A recent observational International Registry of Acute Aortic Dissection (IRAD) study, clearly reported as almost one third of the 2,400 patients with TAAAD included in the analysis suffered from pre or postoperative neurological deficit as cerebral vascular accident, coma or even spinal cord injury (4).

What we would like to know when we deal with TAAAD is how much the technique influences neurological outcomes and how much the dissection itself impairs cerebral functions. Many times patients are referred for emergent operations but despite the lack of a clear evidence of cerebral malperfusion they develop neurological symptoms during the post-operative course, and it is also true the opposite, even less frequently, patients with clear signs of cerebral malperfusion do not develop permanent neurological deficits postoperatively. This is because we don't know how much malperfusion already impaired neurological functions (*Figure 1*).



Figure 1 Angio-CT reconstruction showing a type A aortic dissection with a severe involvement of the epiaortic vessels. CT, computed tomography.

The aim of the current review article is to go over the primary open issues and state of the art for what concern cerebral protection during surgery for TAAAD.

Literature search criteria

Selection of literature articles was performed using PubMed databases from inception to February 2018, using 'surgical treatment of type A aortic dissection' OR 'neurological events in aortic dissection' OR 'cerebral protection in aortic dissection' OR 'malperfusion in type A aortic dissection' OR 'neurological events after aortic dissection' as either keywords or MeSH terms. Case reports, editorial, expert opinion and comment types of publication were excluded as well as review articles because of potential doubling of results. Among series coming from the same group only the most recent ones were considered. Primary endpoints included pre-operatory neurological events, in-hospital death, cerebral protection strategy and postoperative permanent and permanent neurologic dysfunction.

Results

In *Table 1*, it summarized observational single center experience focusing on neurological outcomes after

TAAAD (5-15).

Among the 11 studies identified in this review, antegrade cerebral perfusion (ACP) was the preferred method of cerebral protection ranging from 28% to 100% between different strategies, followed by retrograde cerebral perfusion (RCP) and deep hypothermic circulatory arrest (DHCA) alone. Operative mortality and permanent neurological deficits varies among 5% to 23% and 3% to 19%, respectively.

According to the data from the German Registry of Acute Aortic Dissection type A (GERAADA) 18.5% of 1,558 patients included in the study presented neurologic deficits at presentation (14). Cerebral protection was achieved with hypothermic circulatory arrest alone in 355 (22.8%), unilateral ACP in 628 (40.3%), bilateral ACP (bACP) in 453 (29.1%), and retrograde perfusion in 34 patients (2.2%). Hypothermic circulatory arrest alone resulted in a mortality-corrected permanent neurological dysfunction rate of 11.5%, whereas the rate was 10.0%, for unilateral ACP and 11.0% for bACP. For hypothermic circulatory arrest times superior to 30 minutes there was a profound increase in mortality compared with the ACP groups (P<0.001) (14).

The data presented by Bossone *et al.* (13) from the multicenter IRAD determined the incidence and prognostic impact of stroke in 2,202 patients who were treated either surgically or medically. Stroke was present at arrival in 132 (6.0%) patients. These patients were older (65±12 vs. 62±15 years; P=0.002) and presented more often with shock (14% vs. 7%; P=0.005) and arch vessel involvement at angio-CT (68% vs. 37%; P<0.001) than patients without stroke. As expected, Inhospital complications and mortality [odds ratio (OR) =1.62] were higher among patients with stroke; however, surgical management had a strong independent association with improved survival compare to medical treatment alone (13).

The latest series available on this topic, investigated the predictors and outcomes of stroke in 303 patients with TAAAD undergoing surgical repair (5). The prevalence of permanent postoperative neurologic injuries was 15.8% and multivariable analysis identified the presence of bovine aortic arch (OR =2.33), preoperative cardiopulmonary resuscitation (OR =6.483) and preoperative malperfusion (OR =2.536) as independent predictors for postoperative stroke. The occurrence of stroke had a strong impact on morbidity and was associated with higher rates of postoperative complications and a significantly longer hospital stay (stroke: 23±16 days *vs.* no stroke: 17±18 days; P=0.021) (5).

Author, year	Institution	Study type	Patients	Preoperative neurologic malperfusion, n (%)	Cerebral protection, n (%)	Cannulation site, n (%)	Circulatory arrest time (min)	Operative mortality, n (%)	PND, n (%)	TND, n (%)
Dumfarth, 2018 (5)	Medical University Innsbruck, Innsbruck, Austria	SO	303	17 (5.6)	DHCA: 46 (15.2); SACP: 202 (66.7); RCP: 45 (14.9)	Axillary: 136 (44.9); femoral: 145 (47.9); ascending aorta: 16 (5.3); right carotid artery: 6 (2.0)	44.9±21.3	41 (13.5)	48 (15.8)	NA
Nishida, 2017 (6)	Sakakibara Heart Institute, Tokyo, Japan	SO	702	61 (8.7)	SACP: 242 (34.5); RCP: 460 (65.5)	Axillary: 16 (2.3); femoral: 615 (87.6); ascending aorta: 12 (1.7); apex left ventricle: 60 (8.5)	47.6±29.7	38 (5.4)	76 (10.8)	NA
Furukawa, 2017 (7)	Tsuchiya General Hospital, Hiroshima, Japan	SO	137	12 (8.8)	SACP: 137 (100.0)	Femoral: 137 (100.0)	AN	11 (8.0)	4 (2.9)	NA
Keeling, 2017 (8)	Emory University, Atlanta, GA, USA	SO	342	1 (0.3)	uSACP: 342 (100.0)	Axillary: 342 (100.0)	38.9±19.2	40 (11.7)	25 (7.3)	20 (5.8)
Buonocore, 2016 (9)	Second University of Naples, Naples, Italy	SO	111	0	DHCA: 46 (41.4); SACP: 20 (18.0); RCP: 45 (40.5)	Axillary: 55 (49.6); femoral: 56 (50.4)	47.6±29.7	26 (23.4)	21 (18.9)	8 (7.2)
Omura, 2016 (10)	Kobe University, Kobe, Japan	SO	197	39 (19.8)	SACP: 147 (74.6); RCP: 50 (25.4)	Femoral most preferred (data not reported)	NA	18 (9.1)	7 (3.6)	7 (3.6)
Preventza, 2015 (11)	Baylor College, Houston, TX, USA	SO	157	33 (21.0)	bSACP: 63 (40.1); uSACP: 90 (57.3)	Axillary or innominate most preferred (data not reported)	38.5±19.9	21 (13.4)	19 (12.1)	16 (10.2)
Wiedemann, 2013 (12)	Medical University of Vienna, Vienna, Austria	SO	329	20 (6.1)	DHCA: 116 (35.3); SACP: 91 (27.7); RCP: 122 (37.0)	Axillary or femoral most preferred (data not reported)	30 (range, 12–92)	62 (18.8)	53 (16.1)	3 (0.9)
Bossone, 2013 (13)	IRAD registry	SO	1,863	97 (5.2)	NA	NA	NA	371 (19.9)	NA	NA
Kruger, 2011 (14)	GERAADA Registry, Germany	SO	1,558	289 (18.5)	DHCA: 355 (22.8); bSACP: 453 (29.1); uSACP: 628 (40.3); RCP: 34 (2.2)	NA	22.7±14.3 in DHCA; 37.6±23.6 in bSACP; 32.2±17.9 in uSACP	248 (15.9)	209 (13.4)	AN
Bakhtiary, 2008 (15)	University Hospital Frankfurt, Frankfurt am Main, Germany	SO	120	4 (3.3)	SACP: 120 (100.0)	Axillary: 120 (100.0)	25±12	6 (5.0)	5 (4.2)	3 (2.5)
OS, observa PND, perma Aortic Dissed	tional study; DHCA, d nent neurological defic stion type A; uSACP, u	eep hy cit; TNE inilatera	pothermic), transien al selective	circulatory arrest; S it neurological defici e antegrade cerebra	ACP, selective anteg t; IRAD, International I perfusion; bSACP, I	Irade cerebral perfusion; RCF I Registry of Acute Aortic Dis: oilateral selective antegrade c	, retrograde cerebral p section; GERAADA, G erebral perfusion.	perfusion; N ierman Regi	A, not appli stry of Acut	cable; e

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Discussion

Management of cerebral malperfusion

Historically, brain injury at presentation adversely affected hospital survival of patients with TAAAD (16). Of 1,873 patients with type A dissection enrolled in IRAD, 87 (4.6%) presented with cerebrovascular accident and 54 (2.9%) with coma (17). These patients were more likely to have shock, hypotension, or tamponade (46.8% vs. 25.2%) and arch vessel involvement (55.0% vs. 36.1%). IRAD investigators studied patients by the presence and type of brain injury (no injury vs. stroke vs. coma) and by management treatment (medical vs. surgical). Indeed, the presence of brain injury significantly affected the therapeutic management. Surgery was not performed in 11% of patients without brain injury, 24.1% of patients with cerebrovascular accident, and 33.3% of patients with coma. The reason is likely because cerebral reperfusion and hemorrhagic conversion of the ischemic region might worsen neurologic outcomes and lead to prohibitive postoperative mortality and morbidity rates (16,18).

However, when assessing hospital outcomes according to therapeutic management the authors showed that medical therapy was associated with dismal outcomes: 100% mortality in patients with coma and 76.2% in those with cerebrovascular accident (17). However, surgery led to a hospital survival benefit of 49.6% in patients with preoperative neurologic symptoms and 55.6% of those with coma. Only 12.8% of the medically treated patients with preoperative brain injury survived to discharge compared with 66.7% of those undergoing surgical repair. Moreover 5-year survival of patients presenting with cerebrovascular accident and coma was 23.8% and 0% after medical management vs. 67.1% and 57.1% after surgery (P<0.001).

Czerny and coauthors (19) evaluated the impact of malperfusion syndromes in the GEERADA registry on postoperative neurologic injuries. Out of 2,137 consecutive patients enrolled in the study about 1/3 of the cases experienced signs of pre-operative malperfusion (coronary, cerebral, spinal, visceral, renal, peripheral). The study showed as regardless of pre-operative status, the dissection of supra-aortic branches was an independent predictor of postoperative cerebral injuries with an estimated OR of 2.18.

Indeed, in case of cerebral malperfusion, we still don't have any definitive evidence that a specific surgical strategy or perfusion technique could ameliorate the prognosis of the patients.

In a remarkable comment for the Journal of the American

College of Cardiology, Stewart and Chikwe from the Mount Sinai Hospital in New York suggested to think beyond surgery as in addition to immediate aortic repair, only an aggressive strategies by experienced teams to address ischemia pre-operatively, intra-operatively, or with hybrid therapy should be always considered in this setting (20).

Cerebral protection during aortic arch repair

In order to protect the brain during TAAAD repair, three techniques have been proposed and widely utilized as a means of protecting the brain: DHCA, RCP and antegrade selective cerebral perfusion (ASCP).

However, we are not sure that optimizing cerebral protection allows for safe post-operative outcome. *Figure 2* is showing a complex case of TAAAD in a patient with preoperative signs of cerebral and visceral malperfusion. Of course, our task is to give the best treatment available all the time but we still have a large number of issues for which we have incomplete or no responses at all. Open issues regard the site of arterial cannulation during ACP, the possibility to perfuse unilaterally or bilaterally both hemispheres and how to manage patients with cerebral malperfusion.

While ACP emerged as the preferred perfusion strategy in many centres, the choice of access site for arterial cannulation remains an ongoing topic.

In a recent European survey on current trends in cannulation and neuroprotection-strategies during surgery of the aortic arch, the right subclavian-axillary approach was the favorite site for arterial cannulation (21). Standardization and simplification of cerebral perfusion has favored the axillary artery over the femoral arterial inflow to be the current main access in the case of aortic dissection. Using this advanced approach is possible to simply switch from standard cardio-pulmonary-bypass to unilateral ACP just clamping the innominate artery at the base (21). Axillary cannulation can be performed either directly or via the interposition of an 8 mm vascular prosthesis to optimize haemostasis and reduce the vessel traumatism.

The latest evidence coming from the IRAD registry (22) showed significant improvements during the last 20 years in the outcomes of TAAAD thanks to the advancement in the surgical techniques and confirmed the ACP using the axillary cannulation to be the preferred latest method of cerebral protection.

Another, site of supra-aortic arterial cannulation is represented by the innominate artery but unfortunately is frequently involved in the dissection and therefore not



Figure 2 Angio-CT of patients with (A) type A aortic dissection presenting with signs of cerebral (B) and visceral (C) malperfusion. CT, computed tomography.

suitable for cannulation.

Common carotid artery can be an alternative approach, the experience is limited to only few centres worldwide and it is difficult to give general advice (1). However, in selected patients could be really effective. Short series successfully reported this type of approach in patients with TAAAD having signs of malperfusion (23,24). The additional cannulation of occluded or compressed carotid artery was able to quickly reperfuse the brain and ensure at least unilateral unrestricted cerebral perfusion during cardiopulmonary bypass (CPB). In 2016 Okita et al., reported three interesting cases of patients presenting with brain malperfusion secondary to TAAAD who underwent preoperative perfusion of the right common carotid artery before surgical repair (24). They all arrived at hospital in a comatose or semi-comatose state with left hemiplegia. The right common carotid artery was exposed and directly cannulated using a 12-Fr cannula, a bigger 14-Fr doublelumen cannula was chosen for additional arterial drainage of the right femoral artery (24). The circuit contained a small roller pump (target flow was set at 90 mL/min) and heat exchanger coil. Initial results of this brain-saving system were very promising as all patients survived to arch replacement with minimal postoperative neurological

sequelae (24).

Unilateral vs. bilateral cerebral perfusion strategy

According to the survey of the European Association for Cardio-Thoracic Surgery (EACTS) vascular domain, bACP is now the most frequent method for brain protection in acute presentation (21). However, in more then 1/3 of the cases, unilateral perfusion was used.

Despite the lack of clear evidences in favor of bilateral cerebral perfusion especially in acute scenarios, some relevant reflections should be advanced. First one in the literature, the series on unilateral cerebral perfusion are referred almost always to short times of cerebral perfusion and, for sure, good results are reported.

In a review analysis of Malvindi *et al.* the authors identified 17 papers to answer on whether unilateral ACP is safe as bilateral cerebral perfusion during aortic arch surgery (25). ACP was used in a total of 3,548 patients: bilaterally in 2,949 patients and unilaterally in 599 patients. Both methods of cerebral perfusion resulted in neurological injury rates inferior to 5%, but the period of bACP perfusion was significantly higher (86 to over 164 min) compared to the mean duration (32 min) of unilateral

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cerebral perfusion.

Second issue regarding the open debate on unilateral vs. bilateral cerebral perfusion concern relevant pathophysiologic considerations. One of the most relevant is that cerebral flow gradually declines during cerebral perfusion at each temperature, and this reduction is not the same in every cerebral region (26). This means that there are areas more sensitive to the ischemic injury, like the pons and there are others areas less sensitive, like the hippocampus. Another practical aspect is that: longer is the cerebral perfusion time, higher is the risk of cerebral ischemic injury.

Moreover, we demonstrated (27) with positron emission tomography (PET) scan and magnetic resonance imaging (MRI) that patients undergoing open arch surgery using bilateral cerebral perfusion develop temporary hypometabolism of the occipital lobes as a consequence of an ischemic injury due to the lack of left subclavian artery perfusion and, this hypometabolism is more important and evident for longer period of cerebral perfusion.

In 2017 was published in the *Journal of Thoracic and Cardiovascular Surgery* the only study comparing unilateral *vs.* bilateral cerebral perfusion in 203 patients presenting TAAAD (28). There was no significant difference between groups in terms of CPB, cross-clamp and circulatory arrest times. It failed to demonstrate a significant difference between the two techniques; but looking carefully at the data, bilateral perfusion implied 50% less mortality and neurologic morbidity rates than unilateral perfusion.

In one of the two editorials of this paper (29), the author reported a Hippocrates cite saying, "*Make a habit of two things: to help; or at least do no harm.*" By using bACP, we may achieve both of these goals. Although definitive proof that bACP is superior to unilateral ACP is still lacking: if it does not cause any obvious harm, then why not?

Conclusions

Brain malperfusion caused by acute type A aortic dissection is a silent condition that may not be always clinically evident but impair outcomes regardless of the operative techniques.

Cerebral protection strategies evolved during the years with a clear advantage of ACP using the axillary artery as preferred site of arterial inflow. Although definitive proof that bACP is superior to unilateral ACP is still lacking, there is any obvious harm to use a complete brain protection especially when prolonged periods of ACP are anticipated.

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Footnote

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

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