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Temporary neurological dysfunction after surgery of the thoracic aorta: a predictor of poor outcome and impaired quality of life☆

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Abstract

Background: Transient neurological dysfunction (TND) consists of postoperative confusion, delirium and agitation. It is underestimated after surgery on the thoracic aorta and its influence on long-term quality of life (QoL) has not yet been studied. This study aimed to assess the influence of TND on short- and long-term outcome following surgery of the ascending aorta and proximal arch. **Methods:** Nine hundred and seven patients undergoing surgery of the ascending aorta and the proximal aortic arch at our institution were included. Two hundred and ninety patients (31.9%) underwent surgery because of acute aortic dissection type A (AADA) and 617 patients because of aortic aneurysm. In 547 patients (60.3%) the distal anastomosis was performed using deep hypothermic circulatory arrest (DHCA). TND was defined as a Glasgow coma scale (GCS) value <13. All surviving patients had a clinical follow up and QoL was assessed with an SF-36 questionnaire. **Results:** Overall in-hospital mortality was 8.3%. TND occurred in 89 patients (9.8%). As compared to patients without TND, those who suffered from TND were older (66.4 vs 59.9 years, $p < 0.01$) underwent more frequently emergent procedures (53% vs 32%, $p < 0.05$) and surgery under DHCA (84.3% vs 57.7%, $p < 0.05$). However, duration of DHCA and extent of surgery did not influence the incidence of TND. In-hospital mortality in the group of patients with TND compared to the group without TND was similar (12.0% vs 11.4%; p = ns). Patients with TND suffered more frequently from coronary artery disease (28% vs 20.8%, p = ns) and were more frequently admitted in a compromised haemodynamic condition (23.6% vs 9.9%, $p < 0.05$). Postoperative course revealed more pulmonary complications such as prolonged mechanical ventilation. Additional to their transient neurological dysfunction, significantly more patients had strokes with permanent neurological loss of function (14.6% vs 4.8%, $p < 0.05$) compared to the patients without TND. ICU and hospital stay were significantly prolonged in TND patients (18 ± 13 days vs 12 ± 7 days, $p < 0.05$). Over a mean follow-up interval of 27 ± 14 months, patients with TND showed a significantly impaired QoL. **Conclusion:** The neurological outcome following surgery of the ascending aorta and proximal aortic arch is of paramount importance. The impact of TND on short- and long-term outcome is underestimated and negatively affects the short- and long-term outcome.

Keywords: Thoracic aorta; Neurological dysfunction; Outcome

1. Introduction

Despite numerous advances in surgical techniques and cerebral protection strategies, surgery of the ascending aorta remains a major challenge when the proximal or complete arch has to be addressed. Nevertheless, patient survival and the perioperative incidence of major neurological accidents have developed favourably. In parallel, survival has improved. Logically then, an increasing interest turned to quality of life once these patients return home and/or restart working. Opposite to permanent neurological dysfunctions, which usually correlate with brain CT-scan and/or MRI findings, another more subtle form of neurological injury may develop postoperatively and can be defined as 'temporary neurological dysfunction' (TND). TND consists of postoperative confusion, agitation and delirium, and most probably reflects inadequate brain perfusion or protection during surgery [1,2,9]. It is not typically associated with any structural abnormality, which can be detected by conventional imaging methods. Resolution of the symptoms occurs usually before hospital discharge. Interestingly, several groups recently suggested that TND might be a predictor of long-term functional deficit [2]. Our present study analyses the risk factors for TND and the influence of TND on quality of life (QoL) following surgery of the ascending aorta.

2. Patients and methods

We analysed the data of 907 consecutive patients who underwent surgery of the thoracic aorta during a period of 10

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Table 1
Data are displayed for group 1 without transient neurological dysfunction ($n = 818$), group 2 with transient neurological dysfunction ($n = 89$)

	Group 1 (patients without TND)	Group 2 (patients with TND)	p-Value
Demographics			
Patients	818 (90.2%)	89 (9.8%)	
Age (years)	59.9 ± 13.8	66.4 ± 8.6	<0.01
Male	596 (72.8%)	70 (78.6%)	
Preoperative data			
History of CAD	190 (23.2%)	25 (28.1%)	0.43
Malperfusion preoperative	82 (10%)	20 (22.4%)	<0.01
AADA	248 (30.3)	42 (47.2%)	<0.01
Emergent procedure	263 (32.2%)	47 (52.8%)	<0.01
Haemodynamic compromise	81 (9.9%)	21 (23.6%)	<0.01

CAD indicates coronary artery disease; AADA acute aortic dissection type A. Data are displayed as mean values or absolute values.

years at our institution. Preoperative, intraoperative and postoperative characteristics were collected and are summarised in Table 1. Malperfusion syndrome (MPS) was diagnosed based on clinical symptoms pre- and perioperatively. The same definition for MPS was applied as in a recently published study from our group [15]. TND was defined as a Glasgow coma scale (GCS) value <13, these patients typically present with loss of orientation, slurred language, agitation and no clear response to commands. GCS is assessed on the ICU every 2nd hour and at least three times daily in the wards. All patients with TND required treatment with psychotropic drugs to control agitation and delirium. More subtle forms of neurological dysfunction consisting for example of minimal disorientation and agitation that did not require sedative medication, were not reported as TND in the current study. In contrast to TND we define major stroke as a permanent neurological loss of function with a structural alteration on brain-CT or MRI. We clearly distinguish permanent neurological dysfunction (PND) from TND, an entity in which symptoms in contrast to PND resolve without any specific treatment.

A clinical follow-up including a QoL assessment was performed in all surviving patients using the Short-Form 36 Health Survey Questionnaire (SF-36). Details of this validated questionnaire have been published previously [4,5]. Briefly, SF-36 consists of 36 questions-based evaluations, which reflects QoL in eight different aspects. Results can be compared to an age and gender matched standard population of healthy individuals.

A logistic regression was done including all possible risk factors for TND.

3. Surgical procedures

Surgery was performed in all patients through standard sternotomy and cardiopulmonary bypass was initiated after aortic and right atrial cannulation. In patients with acute aortic dissection type A (AADA), antegrade cerebral perfusion was performed routinely since 2000. Patients in whom the distal anastomosis was planned at the level of the proximal arch, or those in whom the entire arch had to be replaced, body temperature was cooled down between 20 and 24 °C, maximal temperature gradient during cooling and rewarming being 10 °C, target tympanic temperature being between 18 and 20 °C. During the whole study period the cooling and rewarming protocol remained the same.

When DHCA was anticipated, Phenobarbital (15–20 mg/kg) was administered 2–3 min before initiation of DHCA.

Selective antegrade cerebral perfusion (ACP) is performed with oxygenated blood of 12 °C via balloon-blocked catheters placed in the left carotid artery and the innominate artery, with a perfusion pressure of 30–40 mmHg, which corresponds to a flow of 200–300 ml/min. In cases where arterial return of cardiopulmonary bypass is performed through the right axillary artery, antegrade cerebral perfusion is performed using this access (RAACP).

4. Statistical analysis

Data are presented as mean values ± their first standard deviation. A Mann–Whitney U-test and χ^2-test were used for comparison between groups of continuous and nominal variables, respectively. A p value of less than 0.05 was considered significant.

A logistic regression analysis has been performed to compare the influence of the risk factors for TND. We used the Nagelkerkes R-square test to quantify the amount of variance of the dependent variable explained by the model.

5. Results

Among 907 patients included in the current study, 290 (31.9%) underwent surgery because of acute aortic dissection type A (AADA) and 617 (68.1%) because of true aneurysm (Table 1). TND occurred in 89 patients (9.8%) after surgery. A CT-scan of the brain was performed in each one of them and excluded intracerebral bleeding and/or other structural abnormalities. As compared to patients without TND, patients with postoperative TND were older (66.4 vs 59.9 years; $p < 0.05$), and preoperatively in a more compromised haemodynamic condition, mostly because of pericardial tamponade (Table 1). Not surprisingly then, TND appears also to be more associated with preoperative malperfusion syndrome (22.4% vs 10%; $p < 0.05$) in AADA and the need for emergent surgery (Table 1). Cardiopulmonary bypass time was significantly longer in patients with postoperative TND (147.6 ± 49.7 min vs 125.4 ± 56.2 min; $p < 0.05$). Aortic cross-clamping time was however not significantly different between those two groups of patients, nor was the extent of surgery (Table 2). In 547 patients (60.3%) the distal

Table 2
Data are displayed for group 1 without transient neurological dysfunction ($n = 818$), group 2 with transient neurological dysfunction ($n = 89$)

	Group 1 (patients without TND)	Group 2 (patients with TND)	p-Value
Intraoperative data			
Bentall procedure	307 (37.5%)	29 (32.6%)	0.42
Hemi- /total arch	371 (45.4%)	50 (56.2)	0.31
Combined procedure	208 (25.4%)	21 (23.6%)	1
ECC-time	125.4 ± 56.3	147.6 ± 49.7	<0.01
X-clamptime	79.5 ± 34.1	86.8 ± 32.4	0.1
DHCA	472 (57.7%)	75 (84.3%)	<0.01
DHCA-time	21.2 ± 10.9	23.6 ± 12.2	0.13
SACP	204 (24.9%)	28 (31.5%)	0.39

Intraoperative variables, combined procedures are surgery on thoracic aorta in combination with coronary artery bypass grafting and/or surgery on valves other than aortic valve. ECC time indicates extracorporeal circulation time; X-clamptime, aortic cross-clamping time, DHCA time, deep hypothermic circulatory arrest; SACP, selective antegrade cerebral perfusion.

anastomosis was performed during a short period of deep hypothermic circulatory arrest (DHCA). The DHCA time was not significantly different between the groups of patients with TND compared to the group who did not develop signs of TND (Table 2). With longer duration of DHCA the incidence of TND increases. Ninety-nine patients with DHCA duration longer than 30 min (average of 39.5 min) had a trend towards a higher TND rate, compared to the 333 patients with DHCA times shorter than 20 min (average 13.3 min) with an incidence of 18.2% versus 12.0% (p = ns).

In a multivariate analysis assessing the impact of the different risk factors on the development of TND, age, preoperative malperfusion syndrome and the use of DHCA proved to be significant variables to influence TND. A malperfusion syndrome increased the risk for TND by a factor of 2.5. The use of DHCA has an estimated odds ratio for TND of more than three times (Table 3).

In-hospital mortality appeared to be not different between patients with and those without postoperative TND (10.1% vs 8.2%; p = ns). However, a higher morbidity was observed in patients with TND (Table 4). For instance, the incidence of pneumonia (30.3% vs 7.9%; $p < 0.05$) and major stroke (16% vs 6.3%; $p < 0.05$) were significantly higher in these patients. This resulted in prolonged mechanical ventilation as well as longer ICU and hospital stay (Table 4).

Although the strategy of cerebral protection changed during the 10-year interval of this study, subgroup analysis did not reveal any significant difference in the incidence of TND according to the modality of cerebral protection.

Table 4
Data are displayed for group 1 without transient neurological dysfunction ($n = 818$), group 2 with transient neurological dysfunction ($n = 89$)

	Group 1 (patients without TND)	Group 2 (patients with TND)	p-Value
Postoperative data			
In-hospital mortality	67 (8.2%)	9 (10.1%)	0.53
Myocardial infarction	40 (4.8%)	9 (10.1%)	0.04
Pulmonary complication	65 (7.9%)	27 (30.3%)	<0.01
Stroke	39 (4.8%)	13 (14.6%)	0.01
ICU-stay (days)	2.9 ± 4.2	7.2 ± 7.3	<0.01
In-hospital stay (days)	11.9 ± 4.2	18.1 ± 13.3	<0.01

Stroke is defined as permanent neurological loss of function with correlate in brain-CT scan. ICU indicates intensive care unit.

After a mean follow-up time of 27 ± 14 months, all patients were evaluated concerning their actual quality of life. Follow-up was completed in 82% of the survivors. Patients with TND showed a markedly impaired QoL in all but one aspect. Except bodily pain, which was within the values of healthy individuals, all other aspects were impaired and below the normal range. In contrast, patients who did not suffer from TND, the results of the SF-36 were in all eight aspects within the reported range of an age and gender matched standard population (Fig. 1).

6. Discussion

Over the last decade, improvements in surgical, perfusion and anaesthesiological techniques, as well as cerebral protection strategies have led to a decrease of mortality as well as a reduction of the incidence of permanent neurological dysfunction [8–10]. More emphasis has therefore been put on a more subtle form of brain injury, the so-called transient neurological dysfunction (TND). It is widely accepted, that TND represents a functional manifestation of subtle and presumably transient brain injury. Nevertheless mid- and long-term observation have shown that TND may not only play a role in the immediate postoperative course, but may also result in long-term functional deficits as well [1,2]. In contrast to frank strokes, which are usually thought to be caused by gross malperfusion and particulate embolism, TND seems to correlate with the use and the duration of DHCA [1–3]. The latter finding can be confirmed by our study, with an increase of incidence of TND threefold when DHCA was used and a trend of more TND in patients with longer DHCA duration. We observed a reduction of mortality and a positive effect on the incidence of permanent stroke since antegrade

Table 3
Logistic regression analysing the risk factors for postoperative TND

	Parameter estimate B	Standard error	p-Value	Relative hazard exp (B)	95.0% Confidence interval for relative hazard exp (B)	
					Lower boundary	Upper boundary
Age	0.048	0.013	0.00	1.049	1.023	1.077
AADA	0.190	0.314	0.54	1.210	0.654	2.237
Malperfusion	0.981	0.316	0.00	2.667	1.436	4.954
Tamponade	0.669	0.366	0.07	1.953	0.953	4.001
RAACP	−0.206	0.359	0.57	0.814	0.402	1.645
DHCA	1.127	0.439	0.01	3.086	1.305	7.301
Constant	−6.333	0.955	0.00	0.002		

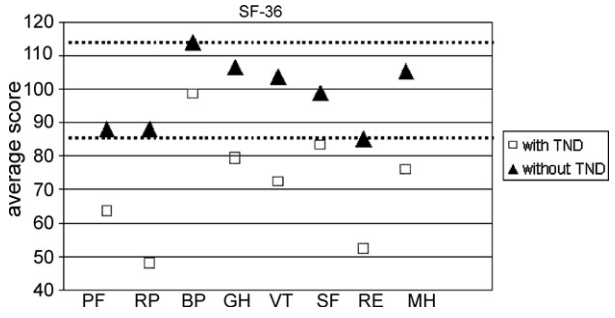

Fig. 1. Influence of transient neurological dysfunction (patients with TND vs patients without TND) on eight aspects of QoL: PF indicates physical functioning; RP physical role functioning; BP bodily pain; GH general health; VT vitality; SF social role functioning; RE emotional role functioning; MH mental health.

cerebral perfusion through right axillary artery has been introduced in clinical routine. In this study though we were not able to show a beneficial effect of selective antegrade cerebral perfusion (SACP) on the incidence of TND. Even if SACP and especially right axillary antegrade cerebral perfusion (RAACP) are accepted strategies to improve brain protection during surgery on the aortic arch, a recent study focussing on cerebral microembolisation measured with transcranial Doppler signal, showed that a small amount of microemboli can be detected during SACP [12].

These microembolisations, most probably do not produce any alteration in brain imaging studies, but might be responsible for transient neurological dysfunction in patients after surgery with the use of SACP.

Age and presence of coronary artery disease (CAD) have previously been described as risk factors for postoperative TND [1,3,7]. This observation is probably related to the fact that increasing age, as well as CAD may be an indicator of cerebrovascular atherosclerosis in these patients, which seems to put them at a higher risk of cerebral dysfunction.

The incidence of TND postoperatively seems to be associated with alcohol abuse. We did not assess alcohol consumption in relation to TND in the present study, due to the difficulty to accurately collecting this data in the clinical setting. Neither referring physicians nor the patients usually mention an increased alcohol intake.

Ergin et al. [2] were able to show that TND is a marker for long-term functional deficit 6 weeks postoperatively.

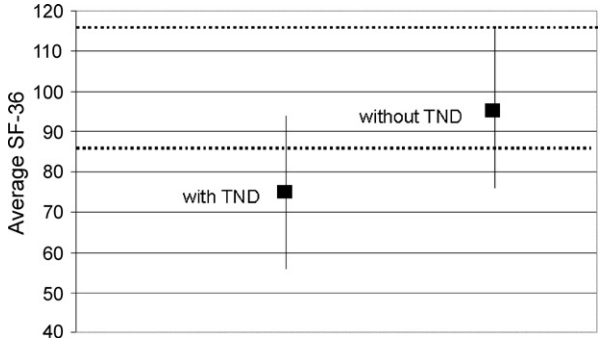

Fig. 2. Influence of transient neurological dysfunction (patients with TND vs patients without TND) on averaged SF-36. Results of standard population are between 85 and 115.

In the present study average follow-up interval was slightly above two years after surgery on the thoracic aorta. Despite this acceptable recovery period, QoL, assessed with the validated.

SF-36 questionnaire, showed a persisting impairment in patients suffering from postoperative TND (Fig. 2). This is in contrast to the patients who showed no signs of TND, who have a preserved QoL in all eight aspects. The results of the SF-36 are adjusted for age and gender and can be compared to a standard population. This allows us to rule out other comorbidities as confounding factors in the follow-up by assuming that morbidities are similarly distributed in an age and gender matched population. Therefore, these results clearly underline that the impact of TND in mid- and long-term outcome is usually underestimated in literature. Every strategy aimed further at optimisation of cerebral protection, inclusively shortening the duration of DHCA, especially in the elderly patient must be applied consequently [14]. The use of selective antegrade cerebral perfusion is probably one of the most important methods to achieve this goal.

We conclude that the impact of TND on short- and long-term outcome is underestimated. Optimising cerebral protection and limitation of the duration of DHCA are important aspects in order to further improve outcome after surgery of the ascending aorta and aortic arch.

References

[1] Ehrlich MP, Schillinger M, Grabenwöger M, Kocher A, Tschernko EM, Simon P, Bohdjalian A, Wolner E. Predictors of adverse outcome and transient neurological dysfunction following surgical treatment of acute type A dissection. Circulation 2003;108:318—23.

[2] Ergin MA, Uysal S, Reich DL, Apaydin A, Lansman SL, McCullough JN, Griepp RB. Temporary neurological dysfunction after deep hypothermic circulatory arrest: a clinical marker of long-term functional deficit. Ann Thorac Surg 1999;67:1887—90.

[3] Fleck TM, Czerny M, Hutschala D, Koinig H, Wolner E, Grabenwöger M. The incidence of transient neurologic dysfunction after ascending aortic replacement with circulatory arrest. Ann Thorac Surg 2003;76:1198—202.

[4] Immer FF, Krähenbühl ES, Immer-Bansi AS, Berdat PA, Kipfer B, Eckstein FS, Saner H, Carrel TP. Quality of life after interventions on the thoracic aorta with deep hypothermic circulatory arrest. Eur J Cardiothorac Surg 2002;21:10—4.

[5] Sullivan M, Karlsson J, Ware JE. SF-36 health survey questionnaire. Swedish manual and interpretation guide. Gothenburg Sweden: Gothenburg University; 1994.

[7] Hagl C, Ergin MA, Galla JD, Lansman SL, McCullough JN, Spielvogel D, Sfeir P, Bodian CA, Griepp RB. Neurologic outcome after ascending aorta-aortic arch operations: effect of brain protection technique in high-risk patients. J Thorac Cardiovasc Surg 2001;121(6):1107—21.

[8] Nakamura K, Onitsuka T, Yano M, Yano Y, Saitoh R, Kojima K, Furukawa K. Predictor of neurologic dysfunction after elective thoracic aorta repair using selective cerebral perfusion. Scand Cardiovasc 2005;39:96—101.

[9] Ehrlich MP, Ergin MA, McCullough JN, Lansman SL, Galla JD, Bodian CA, Apaydin AZ, Griepp RB. Predictors of adverse outcome and transient neurological dysfunction after ascending aorta/hemiarch replacement. Ann Thorac Surg 2000;69:1755—63.

[10] Ergin MA, Galla JD, Lansman L, Quintana C, Bodian C, Griepp RB. Hypothermic circulatory arrest in operations on the thoracic aorta. Determinants of operative mortality and neurological outcome. J Thorac Cardiovasc Surg 1994;107:788—97.

[12] Kamjya H, Klima U, Hagl C, Logemann F, Winterhalter M, Shrestha ML, Kallenbach K, Khaladj N, Haverich A. Cerebral microembolization during antegrade selective cerebral perfusion. Ann Thorac Surg 2006;81:519—21.

[14] Immer FF, Barmettler H, Berdat PA, Immer-Bansi AS, Englberger L, Krähenbühl ES, Carrel TP. Effects of deep hypothermic circulatory arrest

on outcome after resection of ascending aortic aneurysm. Ann of Thorac Surg 2002;74:422—5.
[15] Immer FF, Grobéty V, Lauten A, Carrel TP. Does malperfusion syndrome affect early and mid-term outcome in patients suffering from acute type A aortic dissection? Interact Cardiovasc Thorac Surg 2006;5(2):187—90.

Appendix A. Conference discussion

Dr F. Beyersdorf (*Freiburg, Germany*): I'm sure you are aware of all these studies where also temporary neurological dysfunction have been investigated in cardiopulmonary bypass cases in general. And there were many studies published indicating that cardiopulmonary bypass is disadvantageous in that respect. However other reports have shown that it depends even more importantly on the control group you are using, in order to be able to conclude that cardiopulmonary bypass is associated with some sort of neurological decline.

Can you comment on this for your group of patients? You, of course, compare those patients who had neurological dysfunction temporarily versus those who had none. But then the other question is about the long-term quality of life in patients with that extent of disease in general? But you probably don't have this data I guess.

Dr Krahenbuhl: No, we didn't look at it. But, I mean, you can see that obviously there is a significant difference in the length of total bypass time. So bypass isn't a physiological state for a patient, and it does affect obviously the neurological outcome. But we didn't look especially on that.

Dr R. Griepp (*New York, NY*): I would just have one comment, and perhaps you would like to comment.

I agree with your conclusions. I think the TND, it's important for us to note that, that it does have important implications for what happens to the patient afterwards. But one criticism of your study is that maybe TND was just a marker for patients who had a poor quality of life to begin with. You don't have a preoperative control.

And I think we have to keep that in mind. We want to endeavour to reduce temporary neurological dysfunction, but in any population of patients there are going to be some that enter with a poor neurological function, quality of life, and so on coming into the treatment. And so we have to allow for that in evaluating the results.

Dr Krahenbuhl: But it's true, I mean, these patients were preoperatively worse compared to the other group to start with. So, I agree.

Dr Beyersdorf: Therefore, the kind of control group one is using for comparison is so important.