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Mechanisms of Symptomatic Spinal Cord Ischemia After TEVAR: Insights From the European Registry of Endovascular Aortic Repair Complications (EuREC)

Martin Czerny, MD, MBA[1]; Holger Eggebrecht, MD[2]; Gottfried Sodeck, MD[3]; Fabio Verzini, MD[4]; Piergiorgio Cao, MD[5]; Gabriele Maritati, MD[5]; Vicente Riambau, MD, PhD[6]; Friedhelm Beyersdorf, MD, PhD[7]; Bartosz Rylski, MD[7]; Martin Funovics, MD, PhD[8]; Christian Loewe, MD[8]; Jürg Schmidli, MD[1]; Piergiorgio Tozzi, MD[9]; Ernst Weigang, MD[10]; Toru Kuratani, MD[11]; Ugolino Livi, MD[12]; Giampiero Esposito, MD[13]; Santi Trimarchi, MD[14]; Jos C. van den Berg, MD, PhD[15]; Weiguo Fu, MD, PhD[16]; Roberto Chiesa, MD[17]; Germano Melissano, MD[17]; Luca Bertoglio, MD[17]; Lars Lonn, MD, PhD[18]; Ingrid Schuster, MD[19]; and Michael Grimm, MD[20]

Departments of [1]Cardiovascular Surgery and [3]Cardiology, Inselspital, University Hospital Berne, Switzerland. [2]Department of Cardiology, West-German Heart Center Essen, Germany. [4]Vascular and Endovascular Surgery Unit, Hospital S. Maria Misericordia, Perugia, Italy. [5]Department of Vascular Surgery, San Camillo Hospital, Rome, Italy. [6]Department of Vascular Surgery, Thorax Institute, Hospital Clinic, Barcelona, Spain. [7]Department of Cardiovascular Surgery, Albert-Ludwigs-University Freiburg, Germany. [8]Department of Interventional Radiology, Medical University of Vienna, Austria. [9]Department of Cardiovascular Surgery, CHUV, Lausanne, Switzerland. [10]Department of Cardio-Thoracic and Vascular Surgery, University Medical Center Mainz, Germany. [11]Department of Cardiovascular Surgery, Graduate School of Medicine, Suita, Japan. [12]Department of Cardiopulmonary Science, S. Maria della Misericordia Hospital, Udine, Italy. [13]Città di Lecce Hospital, GVM Hospitals for Care & Research, Lecce, Italy. [14]IRCCS Policlinico San Donato, Cardiovascular Center ''E. Malan,'' Milan, Italy. [15]Service of Interventional Radiology, Ospedale Regionale di Lugano, Switzerland. [16]Department of Vascular Surgery, Zhongshan Hospital, Fudan University, Shanghai, People's Republic of China. [17]Department of Vascular Surgery, Scientific Institute H San Raffaele, Milan, Italy. [18]Department of Vascular Surgery and Cardiovascular Radiology, University of Copenhagen, Denmark. [19]Department of Cardiac Surgery, University of Kosice, Slovakia. [20]Department of Cardiac Surgery, Medical University, Innsbruck, Austria.

Purpose: To test the hypothesis that simultaneous closure of at least 2 independent vascular territories supplying the spinal cord and/or prolonged hypotension may be associated with symptomatic spinal cord ischemia (SCI) after thoracic endovascular aortic repair (TEVAR).

Methods: A pattern matching algorithm was used to develop a risk model for symptomatic SCI using a prospective 63-patient single-center cohort to test the positive predictive value (PPV) of prolonged intraoperative hypotension and/or simultaneous closure of at least 2 of 4 the vascular territories supplying the spinal cord (left subclavian, intercostal, lumbar, and hypogastric arteries). This risk model was then applied to data extracted from the

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Corresponding author: Dr. Czerny, Inselspital, Freiburgstrasse 18, 3010 Berne, Switzerland. E-mail: *martin.czerny@insel.ch*

multicenter European Registry on Endovascular Aortic Repair Complications (EuREC). Between 2002 and 2010, the 19 centers participating in EuREC reported 38 (1.7%) cases of symptomatic spinal cord ischemia among the 2235 patients in the database.

Results: In the single-center cohort, direct correlations were seen between the occurrence of symptomatic SCI and both prolonged intraoperative hypotension (PPV 1.00, 95% CI 0.22 to 1.00, p=0.04) and simultaneous closure of at least 2 independent spinal cord vascular territories (PPV 0.67, 95% CI 0.24 to 0.91, p=0.005). Previous closure of a single vascular territory was not associated with an increased risk of symptomatic spinal cord ischemia (PPV 0.07, 95% CI 0.01 to 0.16, p=0.56). The combination of prolonged hypotension and simultaneous closure of at least 2 territories exhibited the strongest association (PPV 0.75, 95% CI 0.38 to 0.75, p<0.0001). Applying the model to the entire EuREC cohort found an almost perfect agreement between the predicted and observed risk factors (kappa 0.77, 95% CI 0.65 to 0.90).

Conclusion: Extensive coverage of intercostal arteries alone by a thoracic stent-graft is not associated with symptomatic SCI; however, simultaneous closure of at least 2 vascular territories supplying the spinal cord is highly relevant, especially in combination with prolonged intraoperative hypotension. As such, these results further emphasize the need to preserve the left subclavian artery during TEVAR.

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Key words: thoracic aorta, stent-graft, thoracic endovascular aortic repair, complication, spinal cord ischemia, paraplegia, paraparesis, hypotension, hypoperfusion, intercostal arteries, left subclavian artery, risk model

Despite being a story of success from the very beginning, thoracic endovascular aortic repair (TEVAR) was associated with rare, but when present, disastrous and challenging clinical situations, such as retrograde type A dissection, paraplegia, and infection.[1–5] As these events are fortunately the exception and not the rule, knowledge regarding these issues is based merely on sporadic cases even in large aortic centers. As a consequence, the academically driven and non-funded European Registry on Endovascular Aortic Repair Complications (EuREC) was founded in 2002 with the aim of collecting these rare events, merging the data, and finally identifying patterns of these uncommon complications in order to prevent them in the future. The aim of the current study was to identify mechanisms of symptomatic spinal cord ischemia after TEVAR using risk modeling applied to data extracted from the EuREC database.

METHODS

Study Design

The study investigated the hypothesis that simultaneous closure of 2 independent vascular territories supplying the spinal cord and/or prolonged hypotension may be associated with symptomatic spinal cord ischemia, which was defined as new onset of disabling paraparesis or paraplegia up to 48 hours after TEVAR. According to the collateral network theory, the 4 independent vascular territories supplying blood to the spinal cord are the left subclavian, intercostal, lumbar, and the hypogastric arteries.[6] Simultaneous closure of 2 independent vascular territories during TEVAR was defined as overstenting of the intercostal arteries plus at least one other vascular territory, such as the left subclavian artery. Prolonged intraoperative hypotension was defined as a systolic blood pressure <60 mmHg for >5 minutes during the procedure.

Risk Modeling and Model Validation

To overcome the low incidence of this fortunately orphan disease, a risk model was created using a pattern matching algorithm that looked for exact matches between data on post-TEVAR spinal cord ischemia and predefined patterns, in this case simultaneously covering 2 independent vascular territories and/or prolonged intraoperative hypotension. First, the model was used to test the predictive value of these presumptive risk factors in

a prospective single-center cohort whose size was based on the following assumptions. The expected incidence of postoperative paraplegia is ~5%,[7] so at least 60 patients would be necessary to gain meaningful effect sizes (n=3). The proposed risk model was then applied to the multicenter EuREC cohort with post-TEVAR paraplegia to demonstrate generalizability.

Data Sources

The prospective single-center cohort (Table 1) included 63 patients [48 men; median age 70 years, interquartile range (IQR) 64–75]. Seven (11%) patients had undergone previous open heart surgery, and 20 (32%) had previous aortic surgery. Twenty-eight (44%) patients had an underlying diagnosis of atherosclerotic aneurysm, 11 (18%) had an acute type B aortic dissection, 10 (16%) had a chronic aortic dissection, 12 (19%) had a penetrating atherosclerotic ulcer, and the remaining 2 (3%) had an intramural hematoma. A quarter of the patients (15, 24%) were treated in an emergency procedure. In this cohort, 3 (5%) patients experienced symptomatic spinal cord ischemia.

Data on TEVAR complications were extracted from the EuREC database, which contained information supplied by 19 participating European and Asian medical centers. The database was searched to identify all patients undergoing TEVAR for acute or chronic thoracic aortic disease with new onset of symptomatic spinal cord ischemia within the first 48 hours after TEVAR. Patients with preoperative symptomatic spinal cord ischemia were excluded. Intubated patients undergoing TEVAR for traumatic aortic injury were also excluded when the mechanism of injury could not be clearly related to spinal cord ischemia. Patients with new onset of symptomatic spinal cord ischemia beyond 48 hours after TEVAR were excluded as the focus of this work was to study intra- and perioperative factors. In the period 2002 to 2010, 38 (1.7%) cases of symptomatic spinal cord ischemia were reported from among the 2235 patients in the EuREC database. Nearly half of the patients (17, 45%) suffered from immediate symptomatic spinal cord ischemia after TEVAR, whereas neurological symptoms developed within 48 hours in the other 21 cases. Nearly a third of the patients (10, 29%) had cerebrospinal fluid drainage (CSF) before TEVAR vs. 28 patients after onset. Therapeutic blood pressure elevation was performed in 22 (57%) patients. Table 2 compares the demographics, chronic health conditions, risk factors, indications, and outcomes of the 2 patient groups.

TABLE 1
Characteristics of the 63-Patient Single-Center Cohort

Demographics	
Age, y	70 [64–75]
Women	15 (24%)
Chronic health conditions and risk factors	
Hypertension	63 (100%)
Previous cardiac surgery	7 (11%)
Previous aortic surgery	20 (32%)
Morphology	
Atherosclerotic aneurysm	28 (44%)
Acute type B dissection	11 (18%)
Chronic type B dissection	10 (16%)
Penetrating aortic ulcer	12 (19%)
Intramural hematoma	2 (3%)
Procedure	
Emergency	15 (24%)
Cervical rerouting	29 (46%)
Visceral rerouting	3 (5%)
Preoperative CSF drainage	7 (11%)
Number of prostheses	2 (1–3)
Covered aortic length, cm	20 [16–30]
Adverse events	
>1 segment newly occluded	3 (5%)
Prolonged hypotension >5 min	1 (2%)
Neurological event	3 (5%)
Permanent paraplegia	2 (3%)
In-hospital death	2 (3%)

CSF: cerebrospinal fluid.
Continuous data are presented as the mean (range) or median [interquartile range]; categorical data are given as the counts (percentage).

Statistical Analysis

Continuous data are presented as the median and IQR (range from the 25th to the 75th percentile). Discrete data are given as counts and percentages. Comparisons of continuous data between the patient cohorts were performed using the Mann Whitney U test, and categorical data were compared

TABLE 2
Comparison of the Single-Center and EuRec TEVAR Patients With Adverse Neurological Outcomes

	Single Center (n=3)	EuREC (n=35)	p
Demographics			
Age, y	66 [59–71]	70 [62–76]	0.43
Women	0 (0%)	11 (32%)	0.54
Chronic health conditions and risk factors			
Hypertension	3 (100%)	31 (89%)	1.00
Previous cardiac surgery	0 (0%)	2 (6%)	1.00
Previous aortic surgery	0 (0%)	8 (23%)	1.00
Morphology			
Atherosclerotic aneurysm	2 (67%)	18 (51%)	1.00
Type B dissection	1 (33%)	9 (26%)	1.00
Procedure			
Emergency	1 (33%)	17 (49%)	1.00
Rerouting	1 (33%)	10 (29%)	1.00
Preoperative CSF drainage	0 (0%)	10 (29%)	0.55
Number of prostheses	2 (1–3)	2 (1–5)	0.93
Covered aortic length, cm	32 [20–37]	25 [17–32]	0.33
Outcome			
>1 segment newly covered	2 (67%)	17 (49%)	1.00
Prolonged hypotension	1 (33%)	8 (23%)	1.00
Permanent paraplegia	2 (67%)	22 (63%)	1.00
In-hospital mortality	0 (0%)	2 (6%)	1.00

CSF: cerebrospinal fluid.
Continuous data are presented as the mean (range) or median [interquartile range]; categorical data are given as the counts (percentage).

using the Fisher exact test. In a subanalysis, the correlation between time of neurological symptom onset and recovery was tested by calculating the Pearson product-moment correlation coefficient (*r*). A 2-sided $p<0.05$ was considered statistically significant. All calculations were performed with STATA 10.2 for Mac OsX (StataCorp LP, Houston, TX, USA).

For the risk models, results are expressed as positive (PPV) and negative predictive values (NPV), derived using the Bayesian theorem. Correlation was tested using the Cohen kappa coefficient (κ) with 95% confidence interval (CI) calculated in the STATA software (kapci command).[8] A resampling model with 1000 replications was used to confirm the confidence interval. Overall model-fit was performed according to standard procedures. Agreement between the predicted and observed patterns was tested according to the technique of Landis and Koch,[9] in which kappa values were stratified as <0: no agreement, 0 to 0.20: slight agreement, 0.21 and 0.40: fair agreement, 0.41 and 0.60: moderate agreement, 0.61 to 0.80 substantial agreement, and 0.81 to 1 almost perfect agreement.

RESULTS

Risk modeling was performed in 3 steps for the prospective single-center cohort: hypotension alone, simultaneous closure of at least 2 independent vascular territories, and a combination of both. Direct correlations were seen between the occurrence of symptomatic spinal cord ischemia and both prolonged intraoperative hypotension [PPV 1.00 (95% CI 0.22 to 1.00), p=0.04; NPV 0.97 (95% CI 0.96 to 0.97)] and simultaneous closure of at least 2 independent spinal cord vascular territories [PPV 0.67 (95% CI 0.24 to 0.91), p=0.005; NPV 0.98 (95% CI 0.96 to 0.96)]. Previous closure of a single vascular territory (i.e., previous infrarenal replacement or

endovascular repair) was not associated with an increased risk of symptomatic spinal cord ischemia [PPV 0.07 (95% CI 0.01 to 0.16), p=0.56; NPV 0.96 (95% CI 0.94 to 0.99)]. The combination of prolonged intraoperative hypotension and simultaneous closure of at least 2 independent spinal cord supplying territories exhibited the strongest association [PPV 0.75 (95% CI 0.38 to 0.75), p<0.0001; NPV 1.00 (95% CI 0.98 to 1.00)].

Applying the model to the entire EuREC cohort of 38 patients with post-TEVAR symptomatic spinal cord ischemia, there was a substantial to almost perfect agreement between the predicted and observed risk factors (κ=0.77, 95% CI 0.65 to 0.90). Resampling confirmed a narrow confidence interval (95% CI 0.63 to 0.88), supporting the hypothesis that simultaneous closure of at least 2 independent vascular territories and/or prolonged intraoperative hypotension were associated with post-TEVAR symptomatic spinal cord ischemia.

In the subanalysis of the EuREC patient group, complete recovery was achieved in 14 (37%) patients; 9 (24%) had partial recovery, whereas no clinical improvement was observed in 15 (39%) patients. Delayed onset showed a better potential for recovery than immediate onset (p=0.03; r=0.36).

DISCUSSION

Extensive coverage of intercostal arteries by a thoracic stent-graft alone is not associated with symptomatic spinal cord ischemia, as sacrifice of 1 vascular territory supplying the spinal cord is irrelevant. Simultaneous closure of at least 2 vascular territories, however, is highly relevant, especially in combination with prolonged intraoperative hypotension. As such, these results further emphasize preservation of the left subclavian artery during TEVAR.

The incidence of symptomatic spinal cord ischemia after TEVAR is surprisingly low, ranging between 1% and 5%.[7,10,11] While risk factors for this complication have been described, the main focus to date has been on extensive coverage of the descending aorta without invoking other potential risk factors. The idea for the current study arose from clinical observations and from discussions among experts that extensive coverage of the descending aortic alone, irrespective of the underlying pathology, is rarely associated with symptomatic spinal cord ischemia. Furthermore, our own strategy always preserved the left subclavian artery, not because of left upper extremity perfusion, as this is always well maintained by collateral circulation, but to maintain posterior cerebellar perfusion, which resulted in an extremely low rate of paraplegia after TEVAR.[12] As has been demonstrated by others,[6] the left subclavian artery also serves as an important perfusion pathway for the spinal cord and is a substantial component of the collateral network. The few cases of paraplegia we encountered fulfilled the criteria of simultaneous closure of the left subclavian artery (in an emergency setting without any option for preceding transposition) and the intercostal arteries. As the importance of the collateral network, including the subclavian, intercostal, lumbar, and hypogastric arteries, was clearly demonstrated, it was logical to apply this concept to patients with symptomatic spinal cord injury after TEVAR. As corroboration, this pattern was evident in the majority of patients sustaining symptomatic spinal cord injury after TEVAR in the EuREC cohort.

The traditional concept of spinal cord blood supply was via an isolated intercostal artery at the lower thoracic level.[13] However, this view is insufficient to explain the majority of symptomatic spinal cord ischemia cases because some patients with occluded lower thoracic levels may not suffer from paraplegia whereas others with these segments preserved may well show symptomatic spinal cord ischemia. By regarding all 4 vascular territories supplying the spinal cord—left subclavian, intercostal, lumbar, and hypogastric arteries—as equally important, risk modeling found strong associations between simultaneous coverage of 2 of these independent vascular territories, intraoperative prolonged hypotension, and the occurrence of symptomatic spinal cord injury. Interestingly, occlusion of 1 hypogastric artery during vascular access surgery was of equal importance as was the occlusion of the left subclavian artery. These findings also underline the

importance of avoiding intraoperative hypotension because of its direct correlation with symptomatic spinal cord ischemia.

Previous infrarenal replacement has been regarded as a risk factor for paraplegia after TEVAR.[7] In this study, no direct correlation between previous infrarenal replacement and symptomatic spinal cord ischemia was shown. Once again, the explanation for this finding lies in the collateral network theory. Among arteries supplying blood to the spinal cord, the collateral network has a huge potential to adapt to changes in regional blood flow. As such, loss of 1 supplying territory can be accommodated within days, which may thereby reduce the risk for symptomatic spinal cord ischemia to the level of any patient with a regular 4-vessel spinal cord blood supply.[14]

We were not able to identify a different pattern of injury in patients sustaining immediate versus late onset symptomatic spinal cord injury. However, outcomes in these 2 groups differed: patients with late onset neurological symptoms were more likely to recover under treatment with CSF drainage and therapeutic hypertension.[15] The main difference may be that symptomatic spinal cord ischemia in patients with so-called immediate onset is not realized periprocedurally because many of these patients are sedated and intubated for days owing to other reasons. Furthermore, the occurrence of late onset spinal cord ischemia may be due to other factors, such as a low serum hemoglobin level, as well as new onset of atrial fibrillation and resultant hypotension, leading to a deadly triad with hypoperfusion and hypooxygenation.[16] Consequently, a strict perioperative surveillance protocol has to be established and scrupulously maintained.

The treatment options for symptomatic spinal cord ischemia are limited and include decompression of the swelling ischemic spinal cord by CSF drainage and pharmacologically-induced hypertension in order to enhance collateral circulation. Interestingly, the majority of patients in these cohorts did not have CSF drainage prior to TEVAR. There are 2 potential explanations. Firstly, time to insert a CSF drain in the acute setting may be limited, and work flow may be driven more by the hemodynamic situation than by prophylactic considerations. Secondly, many patients require maintenance of antiaggregate or anticoagulation therapy, so the risk of bleeding during CSF drain insertion exceeds the potential benefit.[5]

Limitations

This study was a systematic approach to elucidating a clear and traceable algorithm to understand and prevent symptomatic spinal cord injury during TEVAR. Nevertheless, limitations are numerous. Without doubt, there are patients for whom this hypothesis is not valid and the mechanism of paraplegia remains unclear. As such, this report is not the answer to all questions. Furthermore, institutional factors will always have an unquantifiable influence on such reports.

We are aware that a multivariate regression model represents the gold standard for the development of a risk model, but it requires a large sample volume. However, since spinal cord ischemia represents a rare complication after TEVAR, a conventional approach for development of such a risk model would have taken years to accumulate a sufficient sample volume. Pattern recognition analysis, as applied in our study, represents an acceptable approach to identifying risk patterns for orphan diseases.

Conclusion

Extensive coverage of intercostal arteries by TEVAR alone is not associated with symptomatic spinal cord ischemia, as sacrifice of 1 spinal cord blood supplying vascular territory is irrelevant. Simultaneous closure of at least 2 vascular territories is highly relevant, especially in combination with prolonged intraoperative hypotension. As such, these results further emphasize the need to preserve the left subclavian artery.

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