Neurologic complications after the frozen elephant trunk procedure: A meta-analysis of more than 3000 patients

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ABSTRACT

Objective: The frozen elephant trunk technique's safety regarding spinal cord ischemia has been questioned. We used a meta-analysis to determine the rates of adverse neurologic events and mortality.

Methods: We searched PubMed/Medline, Embase, Scopus, and Cochrane databases (inception to April 2018) to identify studies of neurologic events after the frozen elephant trunk procedure. Separate meta-analyses were conducted with random-effects models to assess frozen elephant trunk associations with spinal cord ischemia, stroke, operative mortality, and all adverse events combined. Subgroup analyses compared outcomes in patients with acute versus nonacute type A dissection and aneurysm and with different extents of coverage.

Results: Thirty-five studies (total N = 3154) met inclusion criteria. The pooled rates of the outcomes of interest were 4.7% (95% confidence interval, 3.5-6.2) for spinal cord ischemia, 7.6% (95% confidence interval, 5.0-11.5) for stroke, and 8.8% (95% confidence interval, 7.0-10.9) for operative mortality. The spinal cord ischemia event rate was higher with stent length 15 cm or greater or coverage to T8 or beyond than with stent length of 10 cm (11.6% vs 2.5%, $P < .001$). Adverse event rates in patients with acute type A aortic dissection versus nonacute dissection or aneurysm were as follows: mortality 9.2% versus 7.6% ($P = .46$), stroke 9.3% versus 6.6% ($P = .51$), and overall adverse events 22.0% versus 16.5% ($P = .41$).

Conclusions: As the frozen elephant trunk procedure becomes more popular, accurate data regarding outcomes are vital. We associated the frozen elephant trunk technique with (nonsignificantly) more adverse events overall in acute type A dissection cases. Stent length of 10 cm was associated with significantly less risk of spinal cord ischemia. Using a stent 15 cm or greater or coverage extending to T8 or farther should be avoided. (J Thorac Cardiovasc Surg 2020;160:20-33)

Visual summary of our meta-analysis of 35 FET studies, with results and subgroup analyses.

Central Message

In FET, 10-cm stent length is advisable; length 15 cm or greater or coverage to or beyond T8 should be avoided to prevent SCI. FET should be used cautiously for acute type A aortic dissection.

Perspective

This meta-analysis of 35 observational studies examines mortality and neurologic outcomes associated with the FET technique in patients who require total arch replacement. Currently, the results represent the best available evidence regarding the outcomes of FET in such patients. Judicious use of the technique is advisable.

See Commentaries on pages 34 and 35.

Traditionally, the elephant trunk (ET) procedure involves 2 stages, and the likelihood of death before the second stage is high.¹⁻⁶ The frozen elephant trunk (FET) procedure is a newer approach designed to treat extensive pathology of

the thoracic aorta in a single stage or by facilitating the second stage of a 2-stage procedure.⁷ Single-center institutional experiences and small series comprise most of the existing reports.⁸

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Abbreviations and Acronyms

CI = confidence interval
 ET = elephant trunk
 FET = frozen elephant trunk
 SCI = spinal cord ischemia

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One of the main drawbacks of this newer approach is its potential association with neurologic events. Neurologic complications such as permanent stroke and spinal cord ischemia (SCI) are the most devastating complications of aortic surgery. The emotional and financial burdens for the patient, the patient's family, and the healthcare system are enormous and have lifelong implications.⁹ This meta-analysis examined the current evidence regarding mortality and neurologic complications, with special focus on SCI, associated with the use of the FET (Video 1).

PATIENTS AND METHODS

Search Strategy

Four databases (EMBASE, PubMed/Medline, Scopus, and Cochrane Library) were searched from their beginning to April 2018 to identify studies of the potential association between the FET approach and new postoperative neurologic symptoms (permanent or transient). The search terms used are listed in Table 1. Only English-language articles were searched. The references of all articles included in the study were examined for further relevant series.

Study Design and Eligibility Criteria

A study was deemed eligible if it described aortic arch procedures performed by the ET technique, either "frozen" or "stented." The definition of FET included a total arch operation. Proximal arch or hemiarch procedures (ie, procedures that did not involve the entire arch) with antegrade or retrograde stent delivery in the descending thoracic aorta were excluded from this analysis. Other inclusion criteria included a description of intra-thoracic aortic arch repair performed via median sternotomy, the baseline characteristics of the patients, and the incidence of permanent or transient SCI, mortality, or permanent or transient stroke, as well as a sample size of 10 or more patients to prevent bias arising from small samples (Figure 1).

When multiple publications by the same authors were identified and study cohorts overlapped, only the latest report was included. Other meta-analysis studies were excluded, as were reports that describe only surgical techniques. Preferred Reporting Items for Systematic Review and Meta-Analysis guidelines were used.¹⁰

The abstracts of all articles were independently assessed by 2 reviewers (O.P. and J.S.C.); if the abstract suggested that the study met the inclusion criteria for our analysis, the full-text article was retrieved. Available data were analyzed, and if the 2 reviewers made different decisions about

whether a given article should be included, a consensus was reached by re-examining the articles with regard to the exclusion and inclusion criteria and the specific techniques described. Data were extracted from abstracts, figures, and tables and entered into Microsoft Excel (Microsoft Corp, Redmond, Wash). In addition, attempts were made to contact the individual authors for any necessary clarifications.

Statistical Analysis

Standard descriptive statistics using meta-analysis software, which allowed us to account for the differing weights of the studies, were used to summarize the demographic, preoperative, intraoperative, and outcome data of the eligible studies. Data are presented as number and percentage or mean with 95% confidence interval (CI), as appropriate. The primary end points of the meta-analysis were stroke, SCI (reported as paralysis, paraplegia, or paraparesis), and operative mortality (within 30 days of surgery or before hospital discharge). The pooled effect estimates were calculated as the weighted mean by using a random-effects model (DerSimonian-Laird), which incorporates between-trial heterogeneity and gives wider and more conservative CIs when heterogeneity is present.¹¹ The analyses were performed after a logit transformation of the data, and the results were expressed as an event rate (%) with a 95% CI.

Two subgroup analyses were performed, using the Z-test to obtain the *P* value comparing the 2 groups. The first one compared outcomes from studies that included only patients with acute type A aortic dissection versus studies that included only patients with nonacute type A dissection and aneurysm to determine whether FET operations yielded different results in these 2 patient populations. The second subgroup analysis compared the results from studies that used only a longer stent (≥ 15 cm or spinal cord coverage to T8 or farther) versus those that used only a shorter (10-cm) stent.

The I^2 statistic, defined as the percentage of total variability across studies attributable to heterogeneity rather than chance, was used to assess statistical heterogeneity. The I^2 value lies between 0% and 100%, and is presented with a 95% CI. We used published guidelines to classify the heterogeneity as low ($I^2 = 25\%$ to 49%), moderate ($I^2 = 50\%$ to 74%), or high ($I^2 > 75\%$).^{12,13} In addition, the prediction interval was calculated to determine the range in which the true effect size would fall in 95% of all populations. The possibility of publication bias was evaluated quantitatively with the Egger test and assessed qualitatively with funnel plots. The funnel plots were constructed by Duval and Tweedie's "trim and fill" method, which offers a more nuanced perspective and estimates how the effect size would shift if the apparent bias were to be removed by imputing the missing studies. All statistical analyses were conducted with Comprehensive Meta-Analysis statistical software (version 3, Biostat Inc, Englewood, NJ).

VIDEO 1. Summary of meta-analysis study of more than 3000 patients in whom the FET technique was used and a discussion of this technique's importance. Video available at: [https://www.jtcvs.org/article/S0022-5223\(19\)32242-1/fulltext](https://www.jtcvs.org/article/S0022-5223(19)32242-1/fulltext).

TABLE 1. Search terms used to identify articles for review

Database	Search terms
PubMed/Medline	Medical Subject Heading (MeSH) terms, search filter [tiab] (title/abstract) and other terms (ot) as follows: “Aortic Aneurysm, Thoracic” [Mesh:NoExp] OR “Aortic Aneurysm, Thoracic/surgery” [Mesh:NoExp] OR “Aorta, Thoracic/surgery” [Mesh] OR “Aneurysm, Dissecting” [Majr:NoExp] OR “Aneurysm, Dissecting/surgery” [Majr:NoExp] OR “elephant trunk” [tiab] OR “elephant trunk” OR “elephant trunk” [ot] AND (“Treatment Outcome” [Mesh] OR “Postoperative Complications” [Mesh] OR “Morbidity” [Mesh] OR “morbidity” [tiab] OR risk*[tiab] OR “patient outcome” [tiab] OR “stroke” [tiab] OR “CVA” [tiab] OR “cerebral vascular accident” [tiab] OR “spinal cord injury” [tiab] OR “Treatment Outcome” [tiab] OR “paraplegia” [tiab] OR “paraparesis” [tiab] OR “neurologic* complications” [tiab] OR “spinal cord ischemia” [tiab] NOT ((Animals NOT Humans)) AND ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR clinical trials as topic [mesh:noexp] OR randomly [tiab] OR trial [ti] NOT (animals [mh] NOT humans)))
Scopus	(TITLE-ABS-KEY ((Stroke OR “cerebral vascular accident” OR “CVA” OR “spinal cord injury” OR “spinal cord ischemia” OR “paraplegia” OR “paraparesis” OR (neurologic* AND complication*))) AND (TITLE-ABS-KEY (“elephant trunk” OR (elephant AND trunk))) AND (LIMIT-TO (LANGUAGE, “English”)))
Embase	‘cerebrovascular accident’/exp OR ‘spinal cord injury’/exp OR ‘spinal cord ischemia’/exp OR ‘paraplegia’/exp OR ‘neurological complication’/exp OR ‘stroke’ OR ‘CVA’ OR ‘cerebral vascular accident’ OR ‘spinal cord injury’ OR paraplegia OR paraparesis OR ‘neurologic* complications’ OR (neurologic* AND complication*) OR ‘spinal cord ischemia’ ‘elephant trunk technique’/exp OR ‘elephant trunk procedure’/exp OR (elephant AND trunk) OR ‘elephant trunk’:ab,ti OR ‘elephant trunk’ AND [english]
Cochrane Library	“elephant trunk”

RESULTS

Study Selection and Characteristics of the Trials

The search yielded 745 articles; 390 were excluded as duplicate or overlapping publications, and 355 were deemed potentially relevant. Another 320 articles were excluded after exclusion criteria were applied (Figure 1). Thus, our analysis included 34 publications that met the criteria for full review (Table 2).¹⁴⁻⁴⁷ One of these publications²⁵ reported on 2 separate cohorts, so we treated it as 2 studies for the purpose of our analyses. Thus, our effective sample size was 35 studies.

The included studies were published between 2002 and 2018, and involved a total of 3154 patients (2274 male, 73.6% [95% CI, 70.6-76.4]) with a mean age of 55.3 years (95% CI, 51.3-59.3) (Table 3). Emergency repair was reported in 33 studies and performed in 1705 patients (53.2%). The mean hospital stay, which was reported in 9 studies, was 15.2 days (95% CI, 14.5-15.83), and the mean follow-up period (based on 15 studies) was 30.4 months (95% CI, 24.3-36.4).

Various stents and devices were used: Jotec E-vita (Jotec GmbH, Hechingen, Germany), stainless steel Gianturco Z (Cook Group, Inc, Bloomington, Ind), Chavan-Haverich Prosthesis (Curative GmbH, Dresden, Germany), Cronus (MicroPort Medical Co, Ltd, Shanghai, China), Thoraflex Hybrid Prosthesis (Vascutek, Terumo, Inchinnan, Scotland, UK), and E-Vita Open and E-Vita Open Plus (Jotec GmbH, Hechingen, Germany). In addition, some investigators used custom-made FET devices with the addition of an intact or modified Gore TAG (WL Gore and Associates, Flagstaff, Ariz), Medtronic Valiant (Medtronic, Santa Rosa, Calif),

or Cook endograft (Cook Group, Bloomington, Ind). Also, another custom-made stent was used that comprised a double-linked 10-bend Z stent sutured into an ultrathin woven Dacron graft. One series used a vascular graft (Yuhengjia Sci-Tech Co Ltd, Beijing, China) with the addition of a single-branch graft (Intervascular InterGard Knitted Graft; Datascope Co, Montvale, NJ).

Neurologic Morbidity

Clinical outcomes, including overall (ie, both permanent and transient) stroke and SCI, (paralysis, paraplegia, or paraparesis) are summarized in Table 4. The rate of overall stroke (temporary and permanent) ranged from 0% to 40.9%, and the rate of any spinal cord adverse event ranged from 0% to 24.0%. The pooled outcome rates (95% CI) with corresponding results of heterogeneity and publication bias are shown in Table 5.

The proportional meta-analysis for overall permanent or transient stroke as reported in 32 studies showed a pooled estimate of 7.6% (95% CI, 5.0-11.5), albeit with high heterogeneity ($I^2 = 88.3\%$) (Figure 2). The prediction interval taking the heterogeneity into account indicated that 95% of the population would be within the range of 2.9% to 12.3%. Publication bias was seen both qualitatively (asymmetry in the funnel plot, with missing studies to the right) and quantitatively (Egger $P = .003$) (Figure 3).

The pooled rate for overall SCI (paralysis, paraplegia, or paraparesis) was 4.7% (95% CI, 3.5-6.2), with $I^2 = 46.3\%$ indicating low heterogeneity (Figure 2). Taking this heterogeneity into account yielded a prediction interval of 2.8% to 6.6%, which is the range into

FIGURE 1. Flow chart showing selection and screening process for articles considered for inclusion in the meta-analysis. FET, Frozen elephant trunk.

which 95% of the population would have been. Publication bias was seen both qualitatively (asymmetry in the funnel plot, with missing studies to the right) and quantitatively (Egger $P = .008$) (Figure 3). All 35 articles reported SCI data.

Operative Mortality

The rate of operative mortality (variously reported as operative, 30-day, and in-hospital mortality) ranged from 0% to 21.6%. One study did not report operative mortality specifically for FET²⁶; for the remaining 34 studies, the total pooled operative mortality rate was 8.8% (95% CI, 7.0-10.9) (Figure 2). The $I^2 = 60.5\%$ indicates moderate heterogeneity. The prediction interval taking the heterogeneity

into account indicated that 95% of the population would be within the range of 6.4% to 11.2%. Publication bias was seen both qualitatively (asymmetry in the funnel plot with missing studies to the right) and quantitatively (Egger $P = .002$) (Figure 3).

Subgroup Analysis

Spinal cord coverage T8 or beyond (or stent length ≥ 15 cm) and spinal cord ischemia. We compared studies performed only in patients with spinal cord coverage T8 or beyond or 15 cm or greater stent length ($n = 6$, 201 patients),^{15,23,32-34,42} with studies performed only in patients with stent length equal to 10 cm ($n = 19$, 1634 patients).^{15,17-19,21,22,24,25,27,28,33,35,37,40-42,45,46} The patients

TABLE 2. Study characteristics

First author (year)	Study period	N	Country	Institution
Usui (2002) ¹⁴	1997-2002	24	Japan	Nagoya University Graduate School of Medicine, Aichi Medical University
Flores (2006) ¹⁵	1996-2004	25	Japan	Hokkaido University Graduate School of Medicine
Shimamura (2008) ¹⁶	1994-2004	126	Japan	Osaka University Graduate School of Medicine, Osaka General Medical Center, Morinomiya Hospital
Li (2009) ¹⁷	2003-2008	31	China	Cardiovascular Institute and Fu Wai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College
Chen (2010) ¹⁸	2004-2009	28	China	Nanjing Cardiovascular Disease Research Institute, Nanjing First Hospital Affiliated to Nanjing Medical University
Sun (2010) ¹⁹	2003-2008	19	China	Cardiovascular Institute and Fu Wai Hospital, Peking Union Medical College, Chinese Academy of Medical Science, Tianjin Cardiovascular Institute and Tianjin Chest Hospital
Lima (2012) ²⁰	2001-2010	31	United States	Heart and Vascular Institute, Cleveland Clinic
Shen (2012) ²¹	2010	38	China	The Second Xiangya Hospital, Central South University
Zhao (2012) ²²	2006-2011	24	China	Beijing Aortic Disease Center; Beijing Institute of Heart, Lung and Blood Vessel Diseases; Beijing Anzhen Hospital, Capital Medical University
Hoffman (2013) ²³	2009-2011	32	Germany	University Hospital RWTH Aachen
Di Marco (2014) ²⁴	2013-2014	11	Italy	S. Orsola-Malpighi Hospital, University of Bologna
Ma (2014) ^{25*}	2003-2012	456	China	Chinese multicenter†
Ma (2014B) ^{25*}	2003-2012	347	China	Chinese multicenter†
Nakamura (2014) ²⁶	1998-2010	51	Japan	University of Miyazaki, Miyazaki Prefectural Nobeoka Hospital
Shi (2014) ²⁷	2006-2011	84	China	First Affiliated Hospital, China Medical University
Xiao (2014) ²⁸	2008-2011	33	China	West China Hospital, Sichuan University Chengdu
Yang (2014) ²⁹	2008-2013	86	China	Affiliated Hospital of Medical College, Qingdao University
Zhang (2014) ³⁰	2002-2010	88	China	Institute of Cardiothoracic Surgery, Changhai Hospital, Second Military Medical University
Dias (2015) ³¹	2009-2013	21	Brazil	Heart Institute of the University of São Paulo Medical School
Hiraoka (2015) ³²	2005-2013	26	Japan	The Sakakibara Heart Institute of Okayama
Katayama (2015) ³³	1997-2011	224	Japan	Hiroshima University Hospital; Hiroshima City Asa General Hospital
Ahmad (2016) ³⁴	2013-2015	14	Germany	Johann-Wolfgang-Goethe University Frankfurt/Main, Frankfurt am Main, Germany
Gong (2016) ³⁵	2014-2015	74	China	Beijing Anzhen Hospital Capital Medical University and Beijing Institute of Heart Lung and Blood Vessel Disease
Leontyev (2016) ³⁶	2005-2014	509	International	E-vita Open Registry‡
Ma (2016) ³⁷	2010-2013	99	China	Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology
Shrestha (2016) ³⁸	2010-2014	100	Germany	Hannover Medical School
Aalaei-Andabili (2017) ³⁹	2010-2015	48	United States	University of Florida

(Continued)

TABLE 2. Continued

First author (year)	Study period	N	Country	Institution
Chen (2017) ⁴⁰	2011-2015	20	China	Beijing Aortic Disease Center, Beijing Anzhen Hospital, Capital Medical University
Hu (2017) ⁴¹	2008-2015	106	China	Renmin Hospital of Wuhan University
Preventza (2017) ⁴²	2010-2015	37	United States	Baylor College of Medicine; Texas Heart Institute; Michael E. DeBakey Veterans Affairs Medical Center; Cleveland Clinic
Verhoye (2017) ⁴³	2009-2015	94	France	French multicenter§
Koizumi (2017) ⁴⁴	2014-2016	30	Japan	Kobe City Medical Center General Hospital
Kreibich (2018) ⁴⁵	2015-2017	14	Germany	University of Freiburg
Ma (2018) ⁴⁶	2013-2015	132	China	Huazhong University of Science and Technology
Roselli (2018) ⁴⁷	2009-2016	72	United States	Cleveland Clinic

N, Number of patients included in the study. *Upper entry, labeled Ma (2014), refers to data from acute cases; lower entry, labeled Ma (2014B), refers to data from chronic cases. †Institutions included Beijing Aortic Disease Center, Beijing Anzhen Hospital of Capital Medical University, Beijing Institute of Heart, Lung and Blood Vessel Diseases, and Beijing Engineering Research Center of Vascular Prostheses; Fu Wai Hospital and Cardiovascular Institute, Chinese Academy of Medical Sciences and State Key Laboratory of Cardiovascular Disease, National Center for Cardiovascular Disease; and Aortic Institute at Yale-New Haven. ‡Institutions included Leipzig Heart Center; West German Heart Centre Essen, University Hospital Essen; Sant'Orsola-Malpighi Hospital; Hospital Hietzing; Queen Elizabeth Hospital Birmingham; Robert Bosch Hospital; Tampere University Hospital Heart Center; Szpital Wojewódzki N2, OddziałKardiochirurgii; and Hospital Clinico, University of Barcelona. §Institutions included Pontchiallou University Hospital, Angers University Hospital, Reims University Hospital, and Louis Pradel University Hospital.

with coverage beyond T8 or stent length 15 cm or greater had a significantly higher incidence of SCI (11.6% [95% CI, 6.1-21.1] vs 2.5% [95% CI, 1.5-4.0], $P < .001$) (Figure E1).

TABLE 3. Summary of patient demographics*

	No. of publications reporting	Total N	% or mean (95% CI)
Total patients	35	3154	–
Age (y)	29	2785	55.3 (51.3-59.3)
Male	33	2274	73.6 (70.6-76.4)
Urgent/emergency	33	1705	53.2 (40.4-65.7)
Smoking	6	158	56.3 (46.2-66.0)
Diabetes	20	248	10.8 (7.6-15.2)
Hypertension	26	2039	75.9 (71.3-79.9)
Renal insufficiency	24	220	9.0 (6.2-13.0)
CAD	19	251	12.0 (7.9-17.9)
COPD	17	273	18.4 (13.3-24.8)
Previous sternotomies	8	75	18.5 (9.7-32.4)
Previous aortic/cardiac complications	12	322	31.5 (19.8-46.0)
Prior stroke	19	158	7.2 (4.7-10.8)
CPB time (min)	29	2619	203.6 (191.7-215.5)
Follow-up (mo)	15	742	30.4 (24.3-36.4)
Hospital stay (d)	9	459	15.2 (14.5-15.8)

CI, Confidence interval; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass. *Numbers are pooled data calculated in meta-analysis software that accounts for the differing weights of the studies.

Acute Type A versus Nonacute Type A and Aneurysm

When we compared studies performed only in patients with acute type A aortic dissection ($n = 12$, 1300 patients)^{21,23,25,27-30,35,37,41,46,47} with studies performed only in patients with nonacute type A dissection and aneurysm ($n = 14$, 741 patients),^{14,15,17,19,22,24-26,34,40,42-45} we found the following results: The pooled mortality rate was 9.2% (95% CI, 6.9-12.4) in the patients with acute type A and 7.6% (95% CI, 4.9-11.4) in the patients with nonacute dissection and aneurysm ($P = .46$). The pooled rate of stroke in these 2 groups was 9.3% (95% CI, 4.5-18.5) and 6.6% (95% CI, 3.1-13.5) ($P = .51$), and the pooled rate of SCI was 2.4% (95% CI, 1.3-4.2) and 5.2% (95% CI, 3.1-8.5) ($P = .05$), respectively (Figure E2).

The incidence of the overall composite adverse outcome (mortality, stroke, and SCI) was 22.0% (95% CI, 13.6-33.6) for the acute type A aortic dissection group and 16.5% (95% CI 9.6-26.7) for the nonacute dissection and aneurysm groups ($P = .41$).

DISCUSSION

Since the original description of extensive aortic replacement using the ET technique by Borst and colleagues,⁴⁸ techniques and technology have continued to develop in an effort to simplify complex aortic repairs. The evidence is ambiguous regarding the value of FET repair for extensive aortic pathologies. Kato and colleagues⁴⁹ introduced the placement of an endovascular prosthesis in the descending thoracic aorta; since then, few single-device hybrid endoprostheses have been used in Europe and Asia. Additionally, custom-made

TABLE 4. Summary of clinical outcomes

First author (year)	N	Overall stroke	Overall SCI/paralysis/ paraplegia	Operative mortality
		% (95% CI)	% (95% CI)	% (95% CI)
Usui (2002) ¹⁴	24	4.2 (0.0-12.2)	12.5 (0.0-25.7)	0.0 (0.0-0.0)
Flores (2006) ¹⁵	25	16.0 (1.6-30.4)	24.0 (7.3-40.7)	12.0 (0.0-24.7)
Shimamura (2008) ¹⁶	126	5.6 (1.6-9.6)	6.3 (2.1-10.6)	5.6 (1.6-9.6)
Li (2009) ¹⁷	31	3.2 (0.0-9.4)	0.0 (0.0-0.0)	6.5 (0.0-15.1)
Chen (2010) ¹⁸	28	10.7 (0.0-22.2)	0.0 (0.0-0.0)	14.3 (1.3-27.2)
Sun (2010) ¹⁹	19	5.3 (0.0-15.3)	0.0 (0.0-0.0)	5.3 (0.0-15.3)
Lima (2012) ²⁰	31	12.9 (1.1-24.7)	12.9 (1.1-24.7)	9.7 (0.0-20.1)
Shen (2012) ²¹	38	0.0 (0.0-0.0)	5.3 (0.0-12.4)	7.9 (0.0-16.5)
Zhao (2012) ²²	24	4.2 (0.0-12.2)	0.0 (0.0-0.0)	4.2 (0.0-12.2)
Hoffman (2013) ²³	32	0.0 (0.0-0.0)	0.0 (0.0-0.0)	3.1 (0.0-9.2)
Di Marco (2014) ²⁴	11	9.1 (0.0-26.1)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Ma (2014) ^{25*}	456	2.9 (1.3-4.4)	2.4 (1.0-3.8)	8.1 (5.6-10.6)
Ma (2014B) ^{25*}	347	0.9 (0.0-1.8)	2.3 (0.7-3.9)	4.3 (2.2-6.5)
Nakamura (2014) ²⁶	51	NR	3.9 (0.0-9.2)	NR
Shi (2014) ²⁷	84	33.3 (23.3-43.4)	0.0 (0.0-0.0)	6.0 (0.9-11.0)
Xiao (2014) ²⁸	33	0.0 (0.0-0.0)	0.0 (0.0-0.0)	18.2 (5.0-31.3)
Yang (2014) ²⁹	86	NR	2.3 (0.0-5.5)	5.8 (0.9-10.8)
Zhang (2014) ³⁰	88	14.8 (7.4-22.2)	0.0 (0.0-0.0)	5.7 (0.8-10.5)
Dias (2015) ³¹	21	4.8 (0.0-13.9)	9.5 (0.0-22.1)	14.3 (0.0-29.3)
Hiraoka (2015) ³²	26	7.7 (0.0-17.9)	11.5 (0.0-23.8)	0.0 (0.0-0.0)
Katayama (2015) ³³	224	2.7 (0.6-4.8)	3.6 (1.1-6.0)	3.6 (1.1-6.0)
Ahmad (2016) ³⁴	14	14.3 (0.0-32.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Gong (2016) ³⁵	74	6.8 (1.0-12.5)	6.8 (1.0-12.5)	12.2 (4.7-19.6)
Leontyev (2016) ³⁶	509	8.1 (5.7-10.4)	7.5 (5.2-9.7)	15.9 (12.7-19.1)
Ma (2016) ³⁷	99	34.3 (25.0-43.7)	0.0 (0.0-0.0)	17.2 (9.7-24.6)
Shrestha (2016) ³⁸	100	9.0 (3.4-14.6)	7.0 (2.0-12.0)	7.0 (2.0-12.0)
Aalaei-Andabili (2017) ³⁹	48	6.3 (0.0-13.1)	4.2 (0.0-9.8)	16.7 (6.1-27.2)
Chen (2017) ⁴⁰	20	NR	5.0 (0.0-14.6)	5.0 (0.0-14.6)
Hu (2017) ⁴¹	106	4.7 (0.7-8.8)	0.0 (0.0-0.0)	7.5 (2.5-12.6)
Preventza (2017) ⁴²	37	5.4 (0.0-12.7)	5.4 (0.0-12.7)	21.6 (8.4-34.9)
Verhoye (2017) ⁴³	94	9.6 (3.6-15.5)	4.3 (0.2-8.3)	11.7 (5.2-18.2)
Koizumi (2017) ⁴⁴	30	10.0 (0.0-20.7)	3.3 (0.0-9.8)	0.0 (0.0-0.0)
Kreibich (2018) ⁴⁵	14	14.3 (0.0-32.6)	0.0 (0.0-0.0)	0.0 (0.0-0.0)
Ma (2018) ⁴⁶	132	40.9 (32.5-49.3)	0.0 (0.0-0.0)	14.4 (8.4-20.4)
Roselli (2018) ⁴⁷	72	2.8 (0.0-6.6)	4.2 (0.0-8.8)	4.2 (0.0-8.8)
All studies (range)	3154	0-40.9	0-24.0	0-21.6

N, Number of patients included in study; SCI, spinal cord ischemia; CI, confidence interval; NR, not reported. *Upper entry, labeled Ma (2014), refers to data from acute cases; lower entry, labeled Ma (2014B), refers to data from chronic cases.

devices have become popular. The expected benefits of FET are 2-fold: It allows debranching of the arch vessels and arch replacement by an open technique and creates an optimal proximal landing zone for thoracic endovascular repair of the remaining descending thoracic aorta,

which can be achieved in the same operative session or in a second stage by retrograde stent delivery. A virtual seal in the descending thoracic aorta also can be achieved. Second-stage repair of the entire thoracoabdominal aorta also can be accomplished by open repair,

TABLE 5. Pooled outcome rates (95% confidence intervals), with corresponding results of heterogeneity and publication bias

Outcome	No. of studies	Pooled rate, % (95% CI)	Heterogeneity I ² % (95% CI) prediction interval	Publication bias Egger test P (1-tailed)
Overall stroke	32	7.6 (5.0-11.5)	88.3 (84.5-91.1) 2.9-12.3	.003
Overall SCI	35	4.7 (3.5-6.2)	46.3 (20.1-63.9) 2.8-6.6	.008
Operative mortality	34	8.8 (7.0-10.9)	60.5 (42.5-72.8) 6.4-11.2	.002

CI, Confidence interval; SCI, spinal cord ischemia.

A

FIGURE 2. Event rates for adverse outcomes. Forest plots show the event rates for (A) overall, persistent, or transient stroke (7.6%; 95% CI, 5.0-11.5); (B) spinal cord injury, including persistent and transient paralysis, paraplegia, and paraparesis (4.7%; 95% CI, 3.5-6.2); and (C) overall, operative, 30-day, or in-hospital mortality (8.8%; 95% CI, 7.0-10.9). The estimate of the event rate of each study corresponds to the middle of the *blue squares*, and the *horizontal line* through the *squares* shows the 95% CI. The summary pooled event rate is represented by the middle of the *solid red diamond*, with the width of the *diamond* representing the 95% CI. CI, Confidence interval.

B

FIGURE 2. Continued

total endovascular repair with custom-made branched endografts, or hybrid repair.

In the present meta-analysis, we reviewed the reported data for 3145 patients from 35 studies, with a focus on mortality and neurologic events associated with this procedure (Figure 4). The 8.8% pooled rate of overall mortality is similar to rates produced by other meta-analyses,^{50,51} although our analysis included only total arch FET procedures, whereas the others^{50,51} included both total arch operations with FET and proximal arch procedures with stenting of the descending thoracic aorta.

This mortality rate, which reflects all emergency (53.2%) and elective cases, is less than the 14.5% rate reported for

conventional ET procedures in a recent systematic review.⁵⁰ One possible explanation is that FET procedures are more likely than conventional ET procedures to be performed in specialized aortic surgery centers with access to specific devices.

We found that the pooled estimate for overall permanent or transient stroke reported in 32 studies was 7.6%, which is similar to what is reported for the conventional ET repair (Figure 4).⁵⁰ However, it is higher than what was reported in the previous FET meta-analyses.^{50,51} This difference can be explained by our including only studies of total arch procedures, which are more complex and lengthy—and thus may incur a higher risk of stroke—than proximal arch or hemiarch procedures. The mode of

FIGURE 2. Continued

cerebral perfusion used in the included studies was variously antegrade cerebral perfusion, retrograde cerebral perfusion, and a combination of both, with the most common being antegrade cerebral perfusion. Various levels of hypothermia were used in the studies. Unfortunately, because the studies varied in the ways in which temperatures were measured (rectal or nasopharyngeal) and reported (mean with standard deviation, mean with range, range only), we were not able to examine the relation between hypothermic temperature and overall stroke risk.

Of the 35 FET studies, 12 included only acute type A aortic dissection cases. The overall composite adverse event rate was slightly higher in the acute type A aortic dissection cases than in the nonacute and aneurysm cases, as were the

rates of operative mortality and stroke (Figure 4). This may reflect the urgency of performing a type A dissection procedure and the complexity of the total arch procedure in these patients, whose preoperative characteristics may include preoperative malperfusion, instability, and occasional poor preoperative neurologic status, which have specific implications for acute type A dissection cases and can drive a dismal outcome. We did notice less SCI overall with the acute dissection cases than with the nonacute dissection and aneurysm cases, maybe because these patients' higher rates of mortality and stroke resulted in fewer of them being evaluated for spinal cord deficit. In addition, the status of patency of the false lumen and its effect on the risk of spinal cord deficit are unknown.

FIGURE 3. Logit event rates for adverse outcomes. Funnel plots show these rates for (A) stroke (11.0%; 95% CI, 7.9-16.0), (B) spinal cord injury (6.1%; 95% CI, 4.6-8.1), and (C) mortality (10.1%; 95% CI, 8.2-12.4). *Blue circles* represent the studies used in the analysis, and *red circles* represent the studies that were imputed with the trim-and-fill method. Note: “Ma (2014)” refers to data from acute cases; “Ma (2014B)” refers to data from chronic cases in the same study.

FIGURE 4. A visual summary of the main points of our study. The overall pooled rates of the outcomes of interest were 4.7% for overall SCI, 7.6% for overall stroke, and 8.8% for operative mortality. Additionally, 2 subgroup analyses were performed: One showed that SCI was significantly more frequent in the patients with longer stents or coverage at or beyond T8. The other subgroup analysis found that the FET technique was associated with higher rates of mortality and stroke in patients with acute type A dissection, and the overall adverse event rate (which included mortality, stroke, and SCI) was higher in these patients, too. *FET*, Frozen elephant trunk; *SC*, spinal cord; *SCI*, spinal cord ischemia.

Paralysis and paraparesis are potentially deadly adverse consequences of thoracic endovascular repair, and they remain a major concern with the FET procedure. Data regarding spinal cord protection from thoracic endovascular aortic repair and open thoracoabdominal procedures⁵² can be used to guide FET procedures. As more data have become available regarding the potential for spinal cord compromise, lessons have been learned and registries have been created^{36,43,53} to capture procedures and outcomes and to examine the association between extensive spinal cord coverage and paralysis or paraparesis.

In the International E-vita Open Registry,⁵³ among 90 patients who underwent procedures for chronic dissection (which was type A in 77% of the cases) of the thoracic aorta, 8 (8.9%) developed SCI. Although no correlation between extensive coverage with the FET and SCI was seen in that study, the rate of SCI was higher in patients whose distal landing zone was at or below T10, and no patient with SCI had stent coverage to less than T8. In our meta-analysis, we saw significantly higher rates of paralysis or paraparesis in patients with coverage at T8 or beyond or a stent length of 15 cm or longer (11.6% vs 2.5%, $P < .001$) compared with a length of 10 cm (Figure 4). We acknowledge that the exact location of the suture line proximal or distal to the left subclavian artery, which could affect thoracic spine coverage, was not consistently clear in the articles included in our analysis. Use of cerebrospinal fluid drainage was reported in only 4 studies,^{27,33,36,43} so we could not determine whether this adjunct was protective. In addition, the relationship between circulatory arrest temperature and spinal cord

injury was not evaluated for the reasons stated earlier. In a general sense, it is worth noting that many of the survivors of FET will later go on to have an open thoracoabdominal repair, and such interventions have had good results.⁵⁴

Study Limitations

This meta-analysis study had several limitations. The studies analyzed were observational, with the inherent bias and lack of uniformity in surgical methodology and reporting. Summarizing observational studies presents challenges, including the risk of bias inherent in these designs in a widely heterogeneous literature. We do not have patient-level data, so we are unable to relate risk factors to the outcomes of interest with any certainty. Spinal cord drainage was not reported in the majority of studies. Specific definitions of chronic and acute dissection were also not reported. Most of the studies did not examine permanent and transient events separately, and no information on race or ethnicity was included. The characterization of acute and chronic dissection was based on the criteria used in each study, with no specification as to timing. A variety of devices were used in these studies, from commercially available single-piece endoprostheses to custom-made FET prostheses. In addition, this study did not examine the outcomes of the FET procedure as a single-stage operation versus the first of 2 stages, with intended completion and re-intervention at the second stage. Survival beyond the operative period also was not examined because it was reported in only 4 studies.

Nevertheless, this meta-analysis is of vital importance because FET is becoming more popular in the surgical

community. In contrast to the other reviews,^{51,52} our analysis included only total arch repairs, emphasizing that for reporting purposes, proximal arch or hemiarch repair in combination with stent-graft placement in the descending thoracic aorta should not be viewed or reported as an FET procedure because the results could be different.

CONCLUSIONS

Reports of the effectiveness of any new procedure or device must be interpreted cautiously because results from the specialized centers where these innovations typically are first used may not reflect how the device will perform elsewhere. This meta-analysis is an effort to evaluate mortality and neurologic events associated with this relatively new but increasingly popular procedure. In cases of acute type A aortic dissection, this technique should be performed with caution. In addition, landing zone at T8 or beyond or a stent graft length of 15 cm or more was a significant predictor of SCI. This is of utmost importance, because industry is developing single-graft endoprostheses to treat extensive aortic pathology.

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Conflict of Interest Statement

Dr Coselli consults for, receives royalties and a departmental educational grant from, and participates in clinical trials for Terumo Aortic; consults and participates in clinical trials for Medtronic, and WL Gore & Associates; and serves as a co-investigator for CytoSorbents. Dr Coselli's work is partly funded by the Cullen Foundation. Dr Preventza consults for, participates in clinical trials for, and has received travel funds from Medtronic, Inc; serves as a consultant for Terumo Aortic and WL Gore & Associates; and has received travel funds from Cook Medical. Dr LeMaire has served as a consultant for Terumo Aortic and Baxter Healthcare; has served as an Advisory Panel Member for Biom'up and Acer Therapeutics; has served as a principal investigator for clinical studies sponsored by Terumo Aortic and CytoSorbents; and has served as a co-investigator for clinical studies sponsored by WL Gore &

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Key Words: frozen elephant trunk, aortic arch, aortic dissection, paraplegia, spinal cord deficit

FIGURE E1. Subgroup analysis: SCI in patients treated with stents 15 cm or greater or spinal coverage T8 or beyond versus patients with 10-cm stent length. In the Forest plot, the estimate of the event rate of each study corresponds to the middle of the *blue squares*, and the horizontal line through the *squares* shows the 95% CI. The subgroup pooled event rates are represented by the middle of the *solid red diamonds*, with the width of the *diamonds* representing the 95% CI. The summary pooled event rate is represented by the middle of the *solid green diamond* with the width of the *diamond* representing the 95% CI and indicates that 11.6% (95% CI, 6.1-21.1) of the patients with stent length 15 cm or greater or coverage T8 or beyond had a spinal cord ischemic event after FET, compared with 2.5% (95% CI, 1.5-4.0) of the patients with stent length 10 cm ($P < .001$). Note: For reference 42 (Preventza 2017), the authors provided additional information not included in the publication. Among the 37 patients, the stent lengths used were 10 cm ($n = 14$), 12.5 cm ($n = 1$), and 15 cm ($n = 22$). SCI occurred in 2 patients with 15-cm stents. *CI*, Confidence interval.

A

FIGURE E2. Subgroup analysis: Outcomes in patients treated for acute type A dissection versus nonacute type A dissection and aneurysm. For these 2 subgroups, respectively, Forest plots show the post-FET event rates for (A) overall, persistent, or transient stroke (9.3% [95% CI, 4.5-18.5]) vs 6.6% [95% CI, 3.1-13.5], $P = .51$); (B) spinal cord injury, including persistent and transient paralysis, paraplegia, and paraparesis (2.4% [95% CI, 1.3-4.2] vs 5.2% [95% CI, 3.1-8.5], $P = .05$); and (C) overall, operative, 30-day, or in-hospital mortality (9.2% [95% CI, 6.9-12.4] vs 7.6% [95% CI, 4.9-11.4], $P = .46$). The estimate of the event rate of each study corresponds to the middle of the blue squares, and the horizontal line through the squares shows the 95% CI. The subgroup pooled event rates are represented by the middle of the solid red diamonds, with the width of the diamonds representing the 95% CI. The summary pooled event rate is represented by the middle of the solid green diamond, with the width of the diamond representing the 95% CI. CI, Confidence interval.

B

FIGURE E2. Continued

C

FIGURE E2. Continued