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EVOLVING PARADIGMS IN AORTIC DISSECTION

FROM MORPHOLOGICAL PREDICTORS TO COMPUTER-AIDED DIAGNOSIS

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BACKGROUND

Aortic dissection, when three-dimensional shape influences outcomes

Aortic dissection is characterized by the partial detachment of the inner layer of aortic wall, leading to the creation of two different channels inside the aorta. Depending on which segment of aorta is involved and on the three-dimensional configuration of the dissection, the prognosis varies from elevated risk of lethal complications to stable course. This wide spectrum of potential evolution reflects the completely different indication for treatment, ranging from emergent surgery to conservative management, based on the deep understanding of the morphology and on clinical presentation. Namely, dissections involving ascending aorta (type A) warrant a highly invasive urgent treatment with cardiopulmonary bypass and possibly deep hypothermic circulatory arrest. On the contrary, among dissections originating distal to the arch (type B), those not presenting complications may be managed conservatively. Between these two extremes, many intermediate clinical pictures exist, in which sometimes the indication for treatment is not univocal. Some uncomplicated type B dissections may present an increased risk profile and thus may benefit from early intervention. Because blood flow characteristics and occurrence of complications are deeply influenced by the morphological configuration that the dissection develops, a thorough understanding of the case-specific three-dimensional shape is crucial in order to judge the prognosis and plan the procedure. Still, in some cases the prediction of an adverse outcome remains a puzzling dilemma.

Endovascular treatment of aortic dissection

During the past two decades, the treatment of type B aortic dissection has been revolutionized by the introduction of thoracic endovascular aortic repair (TEVAR). After its first use for aortic dissection in 1999,[1,2] it has become the mainstay of treatment for complicated dissections. Namely, results of TEVAR in terms of mortality

and morbidity compared favorably with traditional open surgical repair.[3,4,5] In the recent years, its use has been proposed also for uncomplicated dissections, with the aim to prevent evolution and complications in selected cases.[6] The goal of TEVAR is to obtain the complete thrombosis of the false lumen. Many papers have reported on the protective role of complete thrombosis of the false lumen. False lumen thrombosis was in fact associated with a lower rate of aorta-related adverse events in several studies[7,8,9,10,11,12]. Other studies found a direct correlation between aortic enlargement and patency of the false lumen[13,14,15]. Remaining dissection after type A repair is somehow similar to primary type B dissection, and false lumen thrombosis was shown to play a protective role also in this setting[16,17]. Although the complete thrombosis of the false lumen was proven to have a protective role, the role of partial false lumen thrombosis is more controversial. Some papers showed that it is associated with a worse outcome.[18,19] Also the presence of an ulcer-like projection in the context of an otherwise completely thrombosed false lumen was associated with increased rates of adverse events.[20,21] Moreover some authors showed that a saccular configuration of the false lumen was associated with worse outcomes[22,23]. Through an experimental model, it was proven that this configuration gives rise to a pressurization of the false lumen.[24] Additionally, this in vitro experiment suggested that distal tears may act as entries after the proximal entry is occluded. In fact, although TEVAR is usually effective in depressurizing the false lumen and leading to its thrombosis in the acute setting,[25] the success rate in the long run is lower for chronic dissections. In chronic dissections, the dissection membrane is fibrotic and thickened, presenting a lower mobility and poor capacity for remodeling.[26] The absence of remodeling is responsible for the failure in achieving an effective false lumen sealing, resulting in persistence of retrograde flow from distal tears and aortic branches such as intercostal and bronchial arteries.[27] Up to 35% of patients treated with TEVAR for chronic type B dissection present late aortic expansion due to retrograde false lumen flow.[28] For this reason, TEVAR alone is often not sufficient to obtain a definitive treatment of chronic aortic dissection, warranting a strict follow-up surveillance. In case of progression of disease, additional procedures may be necessary to gain the complete exclusion of the false lumen. Fenestrated and branched stent grafts can be used, although the procedure is sometimes challenging and requires custom-made prostheses.[29,30] Moreover, the increased risk of spinal

cord ischemia must be taken into account when an extensive coverage of aorta is planned.[31] A less invasive approach is the embolization of the false lumen at the level of distal descending aorta. In 2003, this approach has been described by Loubert et al as the “cork in the bottle neck “ technique.[32] Many materials have been used since for the embolization of the false lumen, including plugs, glue, coils and iliac occluders.[33] Even though the use of two plugs simultaneously has been reported,[34] cases with a very large false lumen are not suitable for embolization with conventional materials. For this specific purpose, the Candy-Plug technique has been developed. This technique was first described in 2013, using a physician-modified graft.[35] Thereafter, other grafts have been used,[36] and a custom-made device has been introduced.

Open dilemma: when to intervene in uncomplicated cases

Still remains unclear which patients may benefit from an early intervention. Many studies have attempted to use the morphological features of the aorta to predict the evolution of uncomplicated dissections during follow-up. Results are varied and sometimes conflicting. To which extent the morphological features analyzed till now are capable of predicting the outcomes in dissection patients is a matter of debate.

Aim of the study

Acknowledging the need for clearer criteria to identify patients who can benefit from early intervention in uncomplicated type B dissection, we aimed at assessing the state of the art of morphological predictors of adverse outcome in this setting. This was done through a systematic review that extensively reports the current literature on morphological predictors of aortic growth and adverse events in type B dissection. The objective to better define the role of TEVAR in uncomplicated dissection patients was pursued through an up-to-date analysis of data from the most important international registries. Before plunging into the analysis of clinical data, an overview is provided on complicated type B dissections, analyzing epidemiology, prognostic value and surgical options. The analysis of clinical data starts from a comparison of uncomplicated patients treated by best medical therapy alone versus best medical therapy associated with TEVAR. This study, carried out using the International

Registry of Aortic Dissection cohort, aimed to analyze the benefit of TEVAR in uncomplicated patients. Then an analysis of patients from the Global Registry for Endovascular Aortic Treatment was performed to compare outcomes of TEVAR used in complicated versus uncomplicated type B aortic dissection. This analysis aimed to better understand the characteristics of the cohort of uncomplicated patients treated by TEVAR. Moreover, by exploring the feasibility of applying advanced computational technologies in the the study of the vascular morphology, we are confident to contribute in bringing new insights in the interpretation of aortic disease. Advanced semi-automated segmentation algorithms have been applied to computed tomography-angiography imaging of aortic disease in order to extract the three-dimensional shape of aortic lumen. This allowed to produce patient-specific models of aortic disease in a transparent rigid resin through Vat-photopolymerization technique. These models were used for preoperative rehearsal of complex cases by the treating surgeons and to improve the spatial understanding of aortic disease by the surgical trainees and medical students. Finally, insight about novel techniques that will potentially revolutionize the prediction of outcomes based on morphology are presented.

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CHAPTER 1

Current evidence in predictors of aortic growth and events in acute type B aortic dissection

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INTRODUCTION

During the past few decades, there has been an ongoing debate on the possibility to predict the evolution of medically treated acute type B aortic dissection based on morphological or clinical features at presentation. Namely, patients with increased risk of disease progression can take advantage of earlier endovascular or surgical treatment. A variety of clinical and imaging variables have been considered as candidate predictors. The aim of this review is to analyze some of the most debated anatomical predictors within the recent literature, with the purpose to establish their validity based on consistency of results across the different studie**s.**

MATERIALS AND *METHODS*

Search strategy and study selection

A search of the MEDLINE database was performed using the following search terms: “type B aortic dissection” and “acute” or synonyms and “predictor” or synonyms. Results were filtered for studies on humans and english language. Original studies published on peer-reviewed journals up to July 1st 2017 were considered for eligibility.

Titles and abstracts were screened by two reviewers and relevant studies were obtained in full text. Studies that matched the inclusion criteria were included and the references were screened for inclusion of additional studies through cross-referencing. The study eligibility was assessed by the two reviewers independently and disagreement were solved in a consensus meeting.

This review was carried out following the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. Studies were included based on the following criteria: case series including acute type B aortic dissections (presentation within 2 weeks); analysis of morphological predictors of aortic growth (AG), aorta-related adverse events (AE) and mortality. To be eligible, the studies had to analyze at least one candidate predictor included in the following categories: total aortic cross-

sectional size, false lumen cross-sectional size, location and size of proximal entry tear, number of intimal tears, false lumen status in terms of thrombosis, longitudinal extent of the dissection, branch vessels involvement. Studies including only patients undergoing operative treatment in the acute phase, only IMH/completely thrombosed FL, only type A aortic dissection, only patients with connective tissue disorders, studies on mixed populations without separate statistical analysis and studies on chronic dissections were excluded.

Extracted data

Extracted data included authors, journal, year of publication, number of patients, mean follow-up, mean age, sex, inclusion and exclusion criteria (IMH, marfan, complicated, operative treatment, type A) definition of the predictor variables, definition of outcome variables, statistical method used and level of significance.

Outcome variables definition

Eligible studies included different definitions of the outcome variables. Aortic growth was defined as follows: annual growth rate (diameter increase between the first and the last CT-scan divided by the time unit, calculated at maximum diameter or at predetermined levels); aneurysmal change (growth ≥ 6 cm); rapid growth (≥1 cm/12 months or 5 mm/6 months); any growth (various cutoff used, ranging from 0 to 5 mm increase in two different CT-scans).

The definition of AE included one or more of the following: failure of BMT, need for intervention, rupture, retrograde dissection, malperfusion, aneurysmal change, rapid growth, new-onset refractory hypertension or pain, aortic-related death.

The mortality outcome included both mortality overall (MO) and aorta-related (MA)

RESULTS

The search returned 276 outputs. 212 papers were excluded based on the title and abstract, 64 were obtained in full text and additional 23 were excluded because did not match the inclusion criteria. After cross-referencing, additional 10 papers were included, resulting in 51 papers included [1-51]

In total the 51 studies included 8074 patients with a mean follow-up of 45 months (Table I). The mean age was 63 years, and male patients were 68%. Marfan patients were included in 26 studies (mean prevalence 4%), excluded in 12, and this information was not available in 13 studies. Intramural hematoma was an exclusion criterion in 8 studies, while among the 10 studies that included these patients, the mean prevalence was 16%. The remaining studies did not provide any information about the inclusion of IMH. Included patients were only uncomplicated at discharge in 19 studies, initially uncomplicated in 13 and also complicated in 19. Initial medical treatment was the inclusion criterion in 29 studies, while the remaining 22 included also patients treated surgically from beginning. Three studies included patients with remaining type B dissection after type A surgical repair. 33 studies analyzed predictors of aortic event, 11 of aortic growth and 17 of mortality.

forty-four studies analyzed the outcomes after discharge while seven studies were limited to in hospital mortality and *AE.*

Table I. Summary

First author (year)	Population[a]					Inclusion and exclusion criteria[b]						Predicted outcomes	
	Pts	FU (mo) median or mean ±SD	Range	Sex M %	Age, mean±SD or median (range)	IMH %	Mrf %	Acute onset [c]	Compl EX[d]	Primary surg %[e]	Type A %[f]	Outcomes[g]	Definition[h]
Kato 1995	41	38	4-140	71	63.2 (33-83)	NA	EX	14d	BD	0	0	AE	AC, RG, AR; GR
Gysi 1997	187	48±13		NA	NA	NA	5	acute	AP	0	0	AE; MO	IN;
Iguchi 1998	43	52	5-96	77	62.1 (44-79)	NA	NA	14d	BD	0	0	AE	AC (≥50), IN
Marui 1999	101	59	2-125	69	66±12 (32–90)	NA	EX	14d	BD	0	0	AE	AC, RG, AR, RG of ULP (≥5)
Bernard 2001	109	44±46	24-164	74	61±14	NA	8	acute	NE	51%	73	MO	
Genoni 2002	130	50±26		80	61.0±11.2 (23–84)	NA	NA	14d	NE	52%	0	AE; MO	IN, OD
Umana 2002	189	54±56		69	62±13 (25-88)	EX	6	14d	NE	35%	0	AE (H), MO	IN
Suzuki 2003	384	in-hospital		71	65±13	18	3	14d	NE	27%	0	MO (H)	
Sueyoshi 2004	62	49±49	2-192	66	63.3±12.3 (40-83)	NA	EX	acute	BD	0	0	G	GR
Akutsu 2004	110	59		65	64,2	NA	NA	acute	BD	0	0	AE, MO, MA	AR, IN
Onitsuka 2004	76	52±36	3-121	72	65.1±9.9 (40–85)	NA	0	14d	AP	0	0	AE	AD, AR, MP, AC (≥50), RG (≥5)
Kunishige 2006	131	52	0-199	75	68.2 (58–81)	NA	NA	14d	NE	39%	0	AE; MA	AC(55), RG, AR, IN
Tsai 2006	242	28		69	62.1± 12.9	NA	NA	14d	NE	22%	0	MO	
Winnerkvist 2006	66	79	22-179	76	62 (33-80)	21	NA	acute	AP	0	0	AE	AD, AR, RD, AC
Hata 2007	180	51±38		66	64.9±11.5 (33–92)	NA	NE	acute	NE	4%	0	AE	IN, AC
Song 2007	100	53±26		60	53±13	NA	6	acute	NE	51%	51	G	AC
Marui 2007	141	64	1-157	69	68 (32-90)	NA	EX	14d	BD	0	0	AE	AC, AR, HP, MP, RG
Tsai 2007 (NEJM)	201	33		69	60.8±13.9	EX	6	14d	NE	27%	0	MO	
Sakakura 2007	220	in-hospital		71	65.1±11.9	NE	NE	14d	NE	2%	0	AE (H)	OD, IN, AR, MP
Tsai 2007	232	31		69	64.2±16.5	13	3	14d	NE	16	0	AE (H)	IN
Takahashi 2008	43	51±5		67	69.2 ± 1.8	NA	EX	14d	AP	0	0	AE	IN, AR, AD, RG (≥5)
Kitada 2008	78	12		73	70.2	NA	EX	2d	AP	0	0	AE	AR, AC, RG, MP, AD, RD
Kodama 2008	171	27	7-57	65	69.9	17	EX	2d	AP	0	0	AE	AC, AR, RD, RG (>5mm), IN
Chang 2008	55	in-hospital		93	58.3±14.7	NA	NA	acute	NE	NE	0	AE (H)	AD, RG, RD, AR, MP
Sueyoshi 2009	71	49±49	6-120	69	64.4 ±11.9 (40-83)	NA	EX	acute	BD	0	0	G	GR
Trimarchi 2010	365	in-hospital		67	63.5±13.8	11	2	14d	AP	20%	0	MO (H)	
Miyahara 2011	160	45	6-100	77	66.1 18–89	NA	3	14d	BD	0	0	AE	AC, AR, MP, RG, IN,
Weiss 2012	52	in-hospital		90	61±12	NA	EX	acute	NE	69%	0	AE (H)	AR, RD, MP, HP, IN
Loewe 2012	65	24		84	58 (51–65)	NA	NA	acute	NE	31%	0	AE	IN, AR, RD, MP, HP, RG (≥20%)
Evangelista 2012	184	77	6-204	78	56±12.9	EX	14	acute	BD	59%	59	AE	AD, IN
Jonker 2012	191	24	IQR 12-24	69	62.1±13	17	3	acute	BD	0	0	G	GR
Delsart 2013	77	51		87	64±12	14	NE	14d	BD	47%	0	AE, MO	IN
Tolenaar 2013	60	23	3-132	65	59.7 (37-82.6)	EX	NA	7d	BD	0	0	G	GR
Trimarchi 2013	84	20	1-150	NA	NA	NA	NA	7d	BD	0	0	G	GR
Tolenaar 2013	62	22±28	3-32	66	60.3±10.7	EX	EX	7d	BD	0	0	G	GR
Sueyoshi 2013	221	60	0-156	57	62 (25-83)	NA	5	acute	NE	NE	0	AE, MA	AC (≥55), AR, MP, RD
Kudo 2014	117	61±49	1-241	69	68.9±11.3 (38-95)	NA	NA	acute	BD	0	0	AE	IN, MP, AC, RG, AR, RD
Grommes 2014	104	NA		71	65.98±11.2	NA	1	14d	AP	0	0	AE, MO	IN, OD;
Ueki 2014	228	38±31		67	70.4±11.8	NA	1	14d	AP	0	0	AE, MA	AD, IN, AC, RD
Tanaka 2014	103	38±31		67	67.1±13.1	NA	NA	14d	AP	0	0	MO	
Miller 2014	461	NA		62	60 (16-98)	NA	2	acute	NE	NE	0	AE	MP, AC, IN
Tolenaar 2014	1034	in-hospital		65	63.5±14	12	3	acute	NE	34%	0	MO (H)	
Kitamura 2015	224	72±49		75	64.2±12.6 (23–94)	NA	3	10d	NE	NE	0	AE, MO	IN, AR, MP, RD
Durham 2015	200	64±41	1-168	61	63.4±15.2	NA	5	14d	AP	0	0	G	≥5mm increase
Kotelis 2015	24	33	13–58	75	61 (44–77)	EX	EX	14d	BD	0	0	G	GR
Lavingia 2015	117	13	4-23	57	66 ± 12	NA	NA	acute	AP	0	0	AE	IN, AR, RG, AC
Ray 2016	156	44	IQR 25-83	60	60.6±13.6	EX	5	14d	AP	0	0	AE, MO	IN, AR, MP, RG, HP.
Kamman 2016	21	NA		86	57.6±14.0	NA	EX	14d	BD	0	0	G	GR (>0); FLGR (>0)
Valentine 2016	99	25±23		64	60±13.7	NA	3	14d	NE	23%	0	AE	IN, AC, RG, AR, RD, MP
Sailer 2017	83	28	IQR 8-61	70	54.0±15.5	EX	14	acute	BD	0	0	AE	AR, MP, AC, RG, HP
Kamman 2017	219	NA		57	62.3	41	3	14d	BD	0	0	G	GR (>0) (absence)
Total	8074	45		68	63	16	4						

(a) Pts, number of patients; FU (mo), follow-up in months; SD, standard deviation; IQR, interquartile range; M, male; **(b)** IMH, intramural hematoma; Mrf, Marfan; EX, excluded; NE, not excluded (but percentage not specified); NA, information not available; **(c)** Maximum time from symptom onset to admission for inclusion (days); "acute", not better specified. **(d)** Complicated patients excluded: BD, complicated before discharge; AP, complicated at presentation; NE, not excluded; **(e)** Primary surgery; **(f)** Remaining type B after type A repair; **(g)** AE, aortic event; G, aortic growth; MO, mortality overall; MA, mortality aorta-related; (H), in hospital; **(h)** AC, aneurysmal change (mm: ≥60, unless specified); RG, rapid aortic growth (mm/year: ≥10, unless specified); AR, aortic rupture; MP, malperfusion; HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; FLGR, false lumen growth rate; ULP, ulcer-like projection; AD, aorta-related death, OD, overall death.

Aortic cross-sectional size

Aortic cross sectional size is the most investigated morphological predictor of aortic events in TBAD (Table II). Forty studies included in this review analyzed it. It was measured either as largest diameter perpendicular to the center-lumen-line, or as maximum short axis distance in axial view. In some studies, multiple measurements at predefined segments were carried out [2–4]. Despite these minor differences in the measurement of the aortic size, there is a good agreement among the studies about its predictive value for aortic events and mortality. More in detail, in 22 studies it was a positive predictor of aortic growth or aortic event at multivariate analysis, and in other 7 there was an association at univariate analysis. Interestingly, three studies showed a small aortic size to be associated with adverse outcome. [5–7] In 7 studies it was predictive of mortality (4 overall, 3 aorta-related) at multivariate analysis and in other 3 there was univariate association (2 overall, 1 aorta-related). 9 studies did not show a significant association of initial aortic size with any outcome. When treated as a dichotomous variable, the cutoff was set at 40-41 mm in most studies. This value, first adopted in 1995 by Kato et al [1], who observed no aortic growth under this threshold [1], was later confirmed (in 2011 at 40.5 mm by Miyahara et al [8]) through receiver operating characteristic curve analysis20. It is worth noticing that Miller et al performed a subgroup analysis based on height, finding that the 40 mm cutoff was associated with complicated course in patients shorter than 180 cm, but was non-significant for patients taller than 180 cm [9].

Table II. Maximum aortic diameter

First Author (year)	Predictor[a]	Outcome[b]	Definition[c]	Cutoff	Statistical Test	*p* Value[d]	
Sailer 2017	MAD	AE	AC, RG, AR, MP, HP	-	Cox regression	ns	
Kamman 2017	MAD	G	GR (>0) (absence)		Univariate	.034	
Ray 2016	MAD	AE	RG, AR, IN, MP, HP.	45	Cox regression	<.01	**
		M	OD		Cox regression	<.01	**
Kitamura 2015	MAD	AE	AR, IN, MP, RD	-	Cox regression	.039	*
Lavingia 2015	MAD	AE	AC, RG, AR, IN	-	Univariate	.047	
					MANOVA	ns	
Kotelis 2015	MAD	G	GR	40	Mann Whitney U-test	.047	*
Durham 2015	MAD	G	≥5 mm increase	35	Cox regression	<.01	**
Tolenaar 2014	MAD	M (H)	OD	55	Logistic regression	<.001	***
Miller 2014	MAD	AE	AC, IN, MP	40	univariate (<180cm)	.004	
					(>180cm)	ns	
Tanaka 2014	MAD	M	OD	-	Cox regression	ns	
Ueki 2014	TB	AE	AC, IN, RD, AD	-	Cox regression	<.001	***
		M	AD		Univariate	<.001	
					Multivriate	ns (.068)	
Grommes 2014	MAD	AE	IN, OD	40	Cox regression	.004	**
		M	OD		Cox regression	.004	**
Kudo 2014	MAD	AE	AC, RG, AR, IN, MP, RD	40	Cox regression	.0003	***
Tolenaar 2013	ML	G	GR	40	Linear regression	ns	
Trimarchi 2013	ML	G	GR	-	Linear regression	ns	
Delsart 2013	LPA	M	OD	-	Univariate	ns (.07)	
Sueyoshi 2013	MAD	AE	AC (≥55), AR, MP, RD		Cox regression	<.001	***
		M	AD		Cox regression	<.001	***
Jonker 2012	MAD	G	GR	<40	Linear regression	.001	***
Evangelista 2012	MAD	AE	IN, AD	-	Cox regression	.003	**
		M	OD		Cox regression	.008	**
Miyahara 2011	MAD	AE	AC, RG, AR, IN, MP	40	Cox regression	<.0001	***
Sueyoshi 2009	MAD	G	GR	40	Univariate	ns	
Chang 2008	MAD	AE (H)	RG, AR, RD, MP, AD	-	Univariate	.025	
					Logistic regression	ns	
Kitada 2008	MAD	AE	AC, RG, AR, MP, RD, AD	40	Univariate	.013	
					Cox regression	ns (.068)	
Takahashi 2008	MAD	AE	RG (≥5), AR, IN, AD,	40	Cox regression	.0035	**
Tsai 2007	MAD	M	OD	-	Univariate	ns (.08)	
Marui 2007	MAD	AE	AC, RG, AR, MP, HP	40	Cox regression	<.01	**
Song 2007	ML	G	AC	-	Logistic regression	UT<.005 MT<.05	** *
Hata 2007	MAD	AE	AC, IN	40	Logistic regression	.0003	***
		HM	OD		Univariate	.0094	
Sakakura 2007	MAD	AE (H)	AR, IN, MP, OD	-	Logistic regression	.03	*
Winnerkvist 2006	MAD	AE	AC, AR, RD, AD	40	Cox regression	.0184	*
Tsai 2006	MAD	M	OD	-	Univariate	ns (.08)	
Kunishige 2006	MAD	AE	AC(55), RG, AR, IN	45	Cox regression	.004	**
		M	AD		Cox regression	<.001	***
Onitsuka 2004	MAD	AE	AC (≥50), RG (≥5), AR, MP, AD	40	Logistic regression	.04	*
Akutsu 2004	MAD	AE	AR, IN	45	Cox regression	.011	*
		M	AD		Cox regression	.037	*
		M	OD		Cox regression	ns	
Sueyoshi 2004	MAD	G	GR	40	Logistic regression	ns	
Genoni 2002	MAD	AE	IN, OD	45	Log–rank	.008	**
		M	OD		Log–rank	.002	**
Marui 1999	MAD	AE	AC, RG, AR, RG of ULP (≥5)	40	Cox regression	<.001	***
Iguchi 1998	MAD	AE	AC (≥50), IN	40	Cox regression	ns	
Gysi 1997	MAD	AE	IN	48	Cox regression	<.001	***
		M	OD		Cox regression	ns	
Kato 1995	MAD	AE	AC, RG, AR; GR	40	Cox regression	.041	*

(a) MAD, maximum diameter of dissected aorta; ML, aortic diameter measured at multiple levels; TB, aortic diameter measured at tracheal bifurcation; LPA, aortic diameter measured behind the left pulmonary artery; **(b)** AE, aortic event; G, aortic growth; M, mortality; (H), in hospital; **(c)** AC, aneurysmal change (mm: ≥60, unless specified); RG, rapid aortic growth (mm/year: 10, unless specified); AR, aortic rupture; MP, malperfusion; HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; AD, aortic related death, OD, overall death; **(d)** ns, non-significant; UT, upper thoracic aorta; MT, mid thoracic aorta; significance level for multivariate analysis: (*), <.05; (**), <.01; (***), <.001

False lumen cross-sectional size

Many different methods have been used to quantify the false lumen size, either as absolute or as relative to true lumen. The FL cross-sectional area was analyzed in two studies: in the first as ratio of TL to the entire lumen (TL/TL+FL) at the level of maximum diameter (non-significant)1, and in the second as maximal false lumen area (cutoff of 922 mm^2, predictive for in-hospital complications) [10]. Also the FL diameter was studied both as absolute value and as ratio. In 2007 Song et al found the absolute diameter of FL to be predictive of late aneurysmal change (≥ 60 mm), establishing a cutoff value at 22 mm through ROC curve analysis [2]. He also found that the ratio FL diameter/aortic diameter increased during time in patients with aneurysmal change. In an attempt to standardize the way in which the diameter is calculated, Delsart et al specified that it was measured perpendicular to the line passing through the two insertion points of the intimal flap [11]. However, it was found not significant for predicting mortality. FL diameter was reported by Ueki et al as predictor of mortality and AE (the latter only at univariate analysis) [12], and by Ray et al (again with the 22 mm cutoff) as associated with lower intervention-free survival, but not with mortality [13]. Evangelista reported TL compression, defined as diameter ratio TL/TL+FL < 0.25, to be predictive of AE but not mortality [14]. Tolenaar et al found that an increase in TL/FL diameter ratio tended to be associated with decreased aortic growth at univariate analysis [4]. He also introduced a qualitative assessment based on the circular versus elliptical configuration of TL and FL. Circular configuration of TL was significantly associated with decreased growth rate at multivariate analysis. This same classification was used by Kamman et al, who reported an association between circular configuration of TL and absence of aortic growth, although this datum was not included in statistical analysis [15]. Finally, Sailer et al, in 2017 proposed a novel measurement based on the circumferential extent of the false lumen (angular distance in degrees between the two insertion points of the intimal flap), which predicted for AE [16]. This measurement allows to overcome the limitation of intimal flap mobility during the cardiac cycle. A more comprehensive approach to measure FL size was used by Lavingia et al, who found the FL volume and TLV/FLV ratio to predict delayed aortic intervention [17]. He established two cutoff values for this ratio, at < 0.8 (highly predictive for need of aortic intervention) and >1.6 (highly predictive for freedom from intervention) and

performed a subgroup analysis that showed a significantly different growth rate among the three groups.

Table III. False lumen size

Author (year)	Predictor[a]	Outcome[b]	Definition[c]	Statistical test	*p* Value[d]	
Sailer 2017	Angular extent	AE	AC, RG, AR, MP, HP	Cox regression	.003	**
Kamman 2016	Circular vs elliptical	G	GR (>0)	-	-	
Ray 2016	FLD (PA) > 22 mm	AE	RG, AR, IN, MP, HP	Univariate	.04	
		M	OD	Univariate	ns	
	FL area (PA)	AE	RG, AR, IN, MP, HP	Univariate	ns	
		M	OD	Univariate	ns	
Lavingia 2015	FL volume	AE	AC, RG, AR, IN	MANOVA	.037	*
	TL/FL volume ratio			MANOVA	.02	*
Ueki 2014	FLD (TB)	AE	AC, IN, RD, AD	Univariate	.002	
				Cox regression	ns	
		M	AD, OD	Cox regression	.01	*
Tolenaar 2013 (JVS)	TL/FL DR (ML)	G	GR	Linear regression	ns	
	Circular vs elliptical	G	GR	Linear regression	.027	*
Delsart 2013	Maximum FLD	M	OD	Univariate	ns	
Evangelista 2012	TL/(TL+FL) DR > 0.25 (along 2/3 of FL length)	AE	IN, AD	Univariate	.04	
		M	OD	Univariate	ns	
Chang 2008	MFLA ≥ 922 mm^2	AE (H)	AR, RD, MP, AD	Logistic regression	.02	*
Song 2007	FLD > 22 mm (ML)	G	AC	Logistic regression	<.005	**
	FL/(TL+FL) DR	G	GR	ANOVA	<.005	
Kato 1995	TL/(TL+FL) AR (MAD)	G	AC, RG, AR; GR	Univariate	ns	

(a) FLD, false lumen diameter; TL, true lumen; PA, measured at the level of main pulmonary artery; ML, measured at multiple levels; TB, measured at tracheal bifurcation; DR, diameter ratio; MFLA, maximum false lumen area; AR, area ratio; MAD, measured at the level of maximum diameter of dissected aorta; (b) AE, aortic event; G, aortic growth; M, mortality; (H), in hospital; (c) AC, aneurysmal change (≥60 mm); RG, rapid aortic growth(10 mm/year); AR, aortic rupture; MP, malperfusion; HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; AD, aortic related death, OD, overall death; (d) ns, non-significant; significance level for multivariate analysis: (*), <.05; (**), <.01; (***), <.001

Primary entry tear size and location

The entry tear location was found as a significant predictor of aortic growth by Kato et al in 1995 [1]. However, in this study, it was reported just as presence or absence of an ET in the thoracic aorta. In 2002 the presence of an ET in the arch (defined as extending from innominate artery to ligament arteriosus), was found to be associated with a higher rate of surgical intervention [18]. Sueyoshi at al tested the presence of ET in arch as predictor of aortic growth in two different studies, finding it non-significant in 2004 [19] and significant in 2009 [20]. Takahashi et al found no correlation of location of proximal ET in arch versus descending aorta with AE [21]. The same author investigated the role of the site of distal reentry (descending versus abdominal aorta), which was also not significant. More detailed evaluations of the primary ET have been carried out in 2012, when its location on the concavity of aortic arch and its distance from LSA were found to be associated with complicated course (the latter significant only at univariate analysis) [22, 23]. Consistently, Evangelista et al reported the proximal location of primary ET to be predictive for AE, and the primary ET size (≥10 mm size cutoff established through ROC curve analysis) to be associated with higher aortic growth and predictive for AE end mortality [14]. However, this study included also remaining type B dissections after operated type A, which may present a different risk profile compared to primary type B. Indeed, in the first category, but not in the latter, the presence of a patent entry tear have been shown to predict the need for intervention in another study [24]. Tolenaar et al analyzed the effect of the distance in cm from LSA on the aortic growth, which was not significant. However, the subset of patients with one entry tear located within 5 cm of the LSA showed a significantly faster aortic growth [25]. The same cutoff of 5 cm was found to be predictive for AE but not for mortality by Ueki et al [12]. Kitamura et al found the proximal location of ET to be predictive of intervention, but unlike previous studies, they found the location on arch convexity to be associated with worse outcome compared to the concavity [26]. Conversely, later studies didn't detect an association of aortic growth or AE with ET location (including concavity and convexity) and size. [7, 16] Other authors observed some correlation between presence of tear in the arch and AE, but did not include these data in the statistical analysis. [27]

Table IV. Entry tear size and location

First author (year)	Predictor[a]	Outcome[b]	Definition[c]	Statistical test	p Value[d]		
Sailer 2017	ETL (cm from LSA)	AE	AC, RG, AR, MP, HP	Univariate	ns		
	ETL (including OC vs IC)	AE	AC, RG, AR, MP, HP	Univariate	ns		
	ETS	AE	AC, RG, AR, MP, HP	Univariate	ns		
Kamman 2017	ETL (arch)	G	GR (>0)	Univariate	ns		
Kitamura 2015	ETL (OC vs distal)	AE	IN, AR, MP, RD	Cox regression	<.0001	***	+
		M	OD	Cox regression	ns		
	ETL (IC vs OC)	AE	IN, AR, MP, RD	Cox regression	ns		
		M	OD	Cox regression	ns		
Kotelis 2015	ETS	G	GR	Univariate	ns		
Ueki 2014	ETL (≥5 cm from LSA)	AE	AD, IN, AC, RD	Cox regression	.002	**	+
		M	AD, OD	Univariate	ns		
Tolenaar 2013	ETL (cm from LSA)	G	GR (ML)	Linear regression	ns		
	1 ET ≤ 5 cm from LSA			Univariate	.003		+
Loewe 2012	ETL (IC vs OC)	AE	IN, AR, RD, MP, HP, RG (≥20%)	Cox regression	<.05	*	+
Weiss 2012	ETL (cm from LSA in quartiles)	AE (H)	AR, RD, MP, HP, IN	Univariate	.002		+
				Cox regression	ns		
	ETL (IC vs OC)	AE (H)	AR, RD, MP, HP, IN	Cox regression	<.001	***	+
Evangelista 2012	ETL (proximal vs distal)	AE	AD, IN	Cox regression	.03	*	+
		M		Univariate	ns		
	ETS (≥ 10 mm)	AE	AD, IN	Cox regression	<.001	***	+
		M		Cox regression	.001	***	+
Krahenbuhl 2012	ETL (patent vs absent) Type A after repair	AE	IN	Cox regression	.017	*	+
	Type B	AE	IN	Cox regression	ns		
Sueyoshi 2009	ETL (arch)	G	GR>0	Cox regression	.0431	*	+
Takahashi 2008	ETL (arch)	AE	IN, AR, AD, RG (≥5)	Univariate	ns		
Sueyoshi 2004	ETL (arch)	G	GR	Univariate	ns		
Umana 2002	ETL (arch)	AE	IN	Univariate	.02		+
Kato 1995	ETL (patent in thorax vs absent)	AE	AC, RG, AR; GR	Univariate	.001		+

(a) ETL, primary entry tear location; ETS, primary entry tear size; LSA, left subclavian artery; OC, outer curvature of the arch; IC, inner curvature of the arch; **(b)** AE, aortic event; G, aortic growth; M, mortality; (H), in hospital; **(c)** AR, aortic rupture; MP, malperfusion; AC, aneurysmal change (mm: ≥60, unless specified); RG, rapid aortic growth (mm/year: 10, unless specified); HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; AD, aortic related death, OD, overall death; **(d)** ns, non-significant; significance level for multivariate analysis: (*), <.05; (**), <.01; (***), <.001; (+), direct relation; (-), inverse relation.

False lumen patency and saccular formation

The status of the false lumen in terms of thrombosis was investigated in 31 studies included in this review (Table IV). 23 studies showed some significance of this feature, while 8 studies did not find any significant association with the outcomes. The complete thrombosis was found to have a protective role against AE (in 6 studies at multivariate analysis [8, 27–31] and in 6 studies at univariate analysis [1, 21, 32–35]) aortic growth (in 4 studies at multivariate analysis [7, 19, 20, 36] and in 2 at univariate [8, 34]) and mortality (3 studies at multivariate analysis[29 ,31 ,37]). However, inconsistencies are present in terms of definitions and inclusion criteria, as some studies excluded IMH and others did not make a distinction between complete thrombosis of the false lumen and IMH. Some authors identified the presence of an ulcer-like projection (ULP) in the context of a thrombosed false lumen as a predictor of worse outcomes in terms of aortic growth and AE [8, 34, 38]. Also the proximal location of an ULP in descending aorta have shown to be predictive of AE [39]. However, a thorough review of papers reporting on ULP is beyond the aim of this review, as papers reporting only on IMH and completely thrombosed false lumen were excluded. After Tsai et al identified in 2007 the partial thrombosis of the false lumen as a predictor for mortality, this variable has been largely investigated. [40] Trimarchi et al found that partial thrombosis was predictive of aortic growth, while patency and complete thormbosis were not significant. [3] Ueki et al found an association of partial thrombosis with all-cause death and aortic-related death, but not with AE, and none of these associations were significant at multivariate analysis12. Nonetheless, the results are not univocal, as several studies have failed to show a correlation between partial thrombosis and outcomes [4, 5, 7, 9, 15, 34, 41, 42] and one study even found a protective role of partial thrombosis [35]. This was associated with better freedom from intervention compared to false lumen patency, while complete thrombosis was associated also with better freedom from death and intervention and in hospital results [35]. Even in this case, some inconsistencies regarding the definition existed. In particular, some authors included the presence of marginal amount of thrombus in the patent class, while others put it into the partial thrombosis class. Another hint on a possible explanation for such inconsistency of results comes from the concept of saccular formation of the false

Table V. False lumen patency and saccular formation

First author (year)	Predictor[a]	Outcome[b]	Outcome definition[c]	Statistical test	p-Value[d]		
Sailer 2017	P, T, PT	AE	AR, MP, AC, RG, HP	Univariate	ns		
Kamman 2017	P	G	GR (>0)	Univariate	.002		+
	PT	G	GR (>0)	Univariate	ns		
	T	G	GR (>0)	Cox regression	.011	*	-
	IMH	G	GR (>0)	Univariate	<.001		-
Kamman 2016	N. P sections	G	GR (>0)	Logistic regression	ns		
	N. PT sections		GR (>0)	Logistic regression	ns		
Durham 2015	T vs P	G	≥5 mm increase	Cox regression	<.01	**	-
Tolenaar 2014	P, T, PT, IMH	M (H)	OD	Univariate	ns		
Miller 2014	P, T, PT	AE	MP, AC, IN	Univariate	ns		
Tanaka 2014	T vs PT	AE	IN, AC, RG, AR, MP	Univariate	ns		
	PT vs P	AE	IN, AC, RG, AR, MP	Univariate	.04		-
	P vs T	AE	IN, AC, RG, AR, MP	Univariate	<.001		+
	P, T, PT	M	OD	Cox regression	ns		
Ueki 2014	P, T, PT	AE	AD, IN, AC, RD	Univariate	ns		
	PT	M	OD	Univariate	.016		+
	P, T, PT	M	OD	Cox regression	ns		
	PT	M	AD	Univariate	.026		+
	T	M	AD	Univariate	.021		-
	P, T, PT	M	AD	Cox regression	ns		
Kudo 2014	T vs any of P, PT, ULP	AE	IN, MP, AC, RG, AR, RD	Univariate	<.001		-
	ULP	AE	IN, MP, AC, RG, AR, RD	Cox regression	.016	*	+
	T vs rest	G	-	Univariate	<.05		-
	T, PT, P, ULP	M	OD	Univariate	ns		
Tolenaar 2013	P, T, PT	G	GR	Linear regression	ns		
	SAC	G	GR	Linear regression	.001	***	+
Trimarchi 2013	PT vs P	G	GR	Linear regression	.04	*	+
	P vs T; PT vs T	G	GR	Univariate	ns		
Delsart 2013	PT	AE	IN	Univariate	.03		+
	P, T, PT	M	OD	Univariate	ns		
Jonker 2012	IMH	G	GR	Linear regression	.005	**	-
	P, T, PT	G	GR	Univariate	ns		
Miyahara 2011	P or ULP vs T	AE	AC, AR, MP, RG, IN	Cox regression	.029	*	+
	T vs ULP; T vs P	G	GR	Univariate	<.01		-
	ULP vs P	G	GR	Univariate	ns		
Sueyoshi 2009	T vs rest; PT vs P	G	GR	Univariate	<.05		-
	T	G	GR (>0)	Logistic regression	.0047	**	-
	P	G	GR (>0)	Logistic regression	ns		
	PT	G	GR (>0)	Univariate	ns		
	SAC (among PT)	G	GR	Univariate	.007		+
Kodama 2008	IMH	AE	AC, AR, RD, RG (>5mm), IN	Univariate	ns		
Kitada 2008	P	AE	AR, AC, RG, MP, AD, RD	Univariate	ns		
Takahashi 2008	P vs T	AE	IN, AR, AD, RG (>5mm/y)	Univariate	.0132		+
Tsai 2007	T vs P	M	post-discharge death	Cox regression	ns		
	PT vs P	M	post-discharge death	Cox regression	.002	**	+
Marui 2007	P vs T	AE	AC, RG, AR, RG of ULP (>5mm/y)	Cox regression	.024	*	+
Hata 2007	P vs T	AE	IN, AC	Univariate	.0486		+
Sakakura 2007	P vs T	AE (H)	OD, IN, AR, MP	Univariate	.02		+
				Logistic regression	.14		
Winnerkvist 2006	ULP	AE	AD, AR, RD, AC	Cox regression	.0018	**	+
	IMH	AE	AD, AR, RD, AC	Univariate	.02		-
	P	AE	AD, AR, RD, AC	Univariate	ns		
	IMH vs P; IMH vs UPL	G	GR	Univariate	<.05		-
Kunishige 2006	P vs T	AE	AC(55), RG, AR, IN	Cox regression	.018	*	+
	P vs T	M	AD	Cox regression	.029	*	+
Onitsuka 2004	P vs T	AE	AD, AR, MP, AC (≥50), RG (≥5mm/y)	Logistic regression	.001	*	+
Akutsu 2004	P vs T	AE	AR, IN	Cox regression	<.001	***	+
	P vs T	M	AD	Cox regression	.038	*	+
	P vs T	M	OD	Cox regression	ns		
Sueyoshi 2004	P vs T (segments)	G	GR (>0) (segments)	Logistic regression	<.0001	***	+
Suzuki 2003	P, T, PT	M (H)	OD (H)	Univariate	ns		
Bernard 2001	P vs T	M	OD	Cox regression	<.05	*	+
Marui 1999	P vs T	AE	AC, RG, AR, RG of ULP (>5mm/y), IN	Cox regression	.024	*	+
Kato 1995	P vs T (or stagnant)	AE	AC, RG, AR; GR	Univariate	.018		+

(a) P, patency of false lumen (FL); T, FL thrombosis, PT, FL partial thrombosis; IMH, intramural hematoma; ULP, ulcer-like projection; SAC, saccular formation of FL, **(b)** AE, aortic event; G, aortic growth; M, mortality; (H), in hospital; **(c)** AC, aneurysmal change (mm: ≥60, unless specified); RG, rapid aortic growth (mm/year: 10, unless specified); AR, aortic rupture; MP, malperfusion; HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; AD, aortic related death, OD, overall death; **(d)** ns, non-significant; significance level for multivariate analysis: (*), <.05; (**), <.01; (***), <.001; (+), direct relation; (-), inverse relation.

lumen. This concept, based on a speculation by Tsai et al [40], defined as presence of inflow but lack of outflow from the false lumen, has been investigated in two studies, and was shown to be predictive of growth in both cases [4, 20]. This finding suggests that saccular formation, rather then just partial trombosis may play a role in false lumen unstability.

Number of tears, number of branch vessels involved and false lumen outflow

As previously stated, it has been postulated that a single proximal ET is associated with increased false lumen pressurization and increased risk of growth and AE (so-called false lumen saccular formation). Based on this concept, it has been hypothesized that the presence of FL outflow channels decreases the risk of adverse outcomes [16]. These can be identified either as intimal tears or as branch vessels involved (which also are theoretically paired with a corresponding intimal tear. Indeed, the number of ET was protective against aortic growth in two studies. [4, 25] Nonetheless, result are not univocal, as Kotelis et al reported that a higher number of ET was associated with higher growth rate [6]. However, in this study the cutoff was set at > 2 instead of > 1 and the sample size was small. As far as the number of vessels coming off the FL is concerned, this was associated with higher growth rate by Kamman et al, [15] while Sailer et al found the number of intercostal arteries to be protective against AE [16]. The same author developed a method based on BVI to estimate the flow emanating from the false lumen, which was also found to be protective against AE [16].

It must be noted that the number of branch vessels involved was studied also as predictor of early results, and was found to be associated with higher in hospital mortality and complications in two studies, [8, 22] and nonsignificant in other two. [24, 39]

Table VI. Number of tears, number of branch vessels involved and false lumen outflow

First author (year)	Definition[a]	Outcome[b]	Definition[c]	Statistical test	p-Value[d]		
Sailer 2017	nr ET	AE	AR, MP, AC, RG, HP	Univariate	ns		
	FL outflow (ml/min)	AE	AR, MP, AC, RG, HP	Cox regression	.055	*	-
	nr intercostals	AE	AR, MP, AC, RG, HP	Cox regression	.024	*	-
Kamman 2017	multiple ET; VVI; AVI; distal ET	G	GR (>0)	Univariate	ns		
Kamman 2016	VVI	G	FLGR (>0)	Logistic regression	.049	*	+
Kotelis 2015	nr ET≤2	G	GR	Univariate	.0455		-
Tolenaar 2014	VVI	M (H)	OD	Univariate	ns		
Tolenaar 2013 (JVS)	nr ET	G	GR	Linear regression	.005	**	-
	BVI	G	GR	Univariate	ns		
Tolenaar 2013 (ATS)	nr ET >1	G	GR	Univariate	.003		-
Trimarchi 2010	VVI	M (H)	OD	Univariate	ns		
Chang 2008	BVI (VVI, AVI, IVI)	AE (H)	AD, RG, RD, AR, MP	Logistic regression	.004	**	+
Suzuki 2003	BVI (VVI, IVI)	M (H)	OD	Logistic regression	.01	*	+

(a) ET, entry tear; BVI, branch vessel involvement; VVI, visceral vessel involvement; AVI, arch vessel involvement; IVI, iliac vessel involvement; **(b)** AE, aortic event; G, aortic growth; M, mortality; (H), in hospital; **(c)** AC, aneurysmal change (mm: ≥60, unless specified); RG, rapid aortic growth (mm/year: 10, unless specified); AR, aortic rupture; MP, malperfusion; HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; AD, aortic related death, OD, overall death; **(d)** ns, non-significant; significance level for multivariate analysis: (*), <.05; (**), <.01; (***), <.001; (+), direct relation; (-), inverse relation

False lumen longitudinal extent and configuration

The distal extention of the dissection was reported in 13 studies [1, 7, 8, 16, 21, 26–28, 30, 34, 38, 44, 45] (mostly as dichotomuous variable: DeBakey type IIIa vs IIIb), only one of which showed a significant association with outcomes (lower rate of AE and intervention) [26]. On the other hand, the proximal extension to the arch predicted for mortality and surgical intervention in two studies, [18, 45] and was non-significant in another two. [46, 47] Conversely, Kamman et al found the proximal extension at the level of LSA (vs arch and descending) to be associated with higher aortic growth rate. [7] The location of FL in the inner vs outer curvature of the arch was also found to predict for growth. [48] Besides, the longitudinal extent in cm was associated with in hospital mortality [10] and late aortic growth [15] on univariate analysis, but these results were not confirmed at multivariate analysis. Other false lumen features analyzed include straight vs spiral configuration (nonsignificant) [4], and presence of multiple false lumina (predictive for aorta-related mortality [47] but not for AE [16, 47]).

Table VII. False lumen longitudinal extent and configuration

First author (year)	Predictor[a]	Outcome[b]	Definition[c]	Statistical test	p-Value[d]		
Sailer 2017	DL, DE, PE, IC vs OC, MFL	AE	AR, MP, AC, RG, HP	Univariate	ns		
Kamman 2017	PE (LSA vs arch and descending)	G	GR (>0)	Univariate	.011		+
	DE	G	GR (>0)	Univariate	ns		
Kamman 2016	DL	G	GR (>0)	Univariate	.002		+
	N. patent FL secitions	G	FLGR (>0)	Logistic regression	.066		+
Valentine 2016	PE	AE	IN, AC, RG, AR, RD, MP	Logistic regression	<.05	*	+
	DE (Thoracic, abdominal, pelvic)	AE		Univariate	ns		
Kitamura 2015	DE	AE	IN, AR, MP, RD	Univariate	.0039		-
Kudo 2014	DE	AE	IN, MP, AC, RG, AR, RD	Univariate	ns		
Tolenaar 2013 (JVC)	PE (IC vs OC)	G	GR	Linear regression	.019	*	-
	Spiral vs straight	G	GR	Univariate	ns		
Sueyoshi 2013	PE	AE	AC (≥55), AR, MP, RD	Univariate	ns		
	MFL			Univariate	ns		
				Cox regression	ns		
	MFL	M	AD	Cox regression	<.0001	***	+
Miyahara 2011	DE	AE	AC, AR, MP, RG, IN,	Univariate	ns		
Chang 2008	DL	AE (H)	AD, RG, RD, AR, MP	Univariate	.004		+
				Logistic regression	ns		
Takahashi 2008	DE	AE	IN, AR, AD, RG (≥5)	Univariate	ns		
Tsai 2007	PE	AE (H)	IN	Univariate	ns		
Marui 2007	DE	AE	AC, AR, HP, MP, RG,	Univariate	ns		
Winnerkvist 2006	DE	AE	AD, AR, RD, AC	Univariate	ns		
Onitsuka 2004	DE	AE	AD, AR, RD, AC	Univariate	ns		
Umana 2002	PE	AE (H)	IN (surgical)	Logistic regression	<.05	*	+
	PE	M	OD	Cox regression	.001	***	+
Marui 1999	DE	AE	AC, RG, AR, RG of ULP (≥5)	Univariate	ns		
Iguchi 1998	DE	AE	AC (≥50), IN	Univariate	ns		
Kato 1995	DE	AE	AC, RG, AR; GR	Univariate	ns		

(a) DE, distal extension (DeBackey IIIa vs IIIb unless specified); DL, dissection length (cm); PE proximal extension (arch vs descending unless specified); IC, inner curvature of the arch; OC, outer curvature of the arch; MFL, multiple false lumina; LSA, left subclavian artery; **(b)** AE, aortic event; G, aortic growth; M, mortality; (H), in hospital; **(c)** AC, aneurysmal change (mm: ≥60, unless specified); RG, rapid aortic growth (mm/year: ≥10, unless specified); AR, aortic rupture; MP, malperfusion; HP, new-onset refractory hypertension or pain; RD, retrograde o repeat dissection; IN, intervention needed; GR, growth rate; FLGR, false lumen growth rate; AD, aortic related death, OD, overall death; **(d)** ns, non-significant; significance level for multivariate analysis: (*), <.05; (**), <.01; (***), <.001; (+), direct relation; (-), inverse relation.

DISCUSSION

Aortic size is the most investigated of all morphological predictors, both as continuous and categorical variable (≥40 mm cutoff). With a good consistency among the studies, it predicts the risk of AE and death in the early and late phase. However even under 40 mm the risk of aortic growth has to be considered, as shown by three different studies [5–7]. Moreover, care must be taken when evaluating a patient taller than 180, as the cutoff of 40 mm ceased to be significant for this subgroup of patients in one study [9].

Although less investigated than aortic diameter, FL size seems to be an important prognostic factor, with a fairly good consistency of results across the studies. Its measurement has been approached in many different ways. Cutoff values have been established both for diameter (≥22 mm) and for area (922 mm2). The compression of TL by the FL is a sign of FL pressurization, which in turn is considered to drive aortic growth and complications. For this reason, it seems meaningful to look at the FL size as relative to TL. This was made by calculating diameter ratios or by a qualitative assessment of FL and TL circular versus elliptical shape. One limitation of these measurements is intrinsic to the imaging technique itself. In fact, the flap is mobile in the acute setting and the relative size of the lumina varies across the cardiac cycle. However a solution to this issue has been recently proposed: in order to minimize this variability, the FL extension is measured as angular distance between the two insertion points of the flap. [16] Another promising technique is the measurement of TLV/FLV ratio, which is still difficult to transfer to clinical practice until the culture of advanced measurements does not circulate among imaging professionals. [17]

The proximal location of the primary entry tear predicted growth or AE in some studies, but was not confirmed by others. Some studies indicated as cutoff 5 cm from LSA, while others used the ligamentum arteriosum as landmark. The role of the location in the inner or outer curvature of the arch is unclear, as few studies investigated this feature, with conflicting results. It has been suggested that this inconsistency may reflect a selection bias due to variability in the time from the onset of symptoms to the time of referral and diagnosis. Namely some of these dissection may present lethal complications or evolve in type A in the acute phase.49

The size of proximal entry tear larger than one cm was reported to predict AE in a study on a mixed population of pure type B aortic dissections and remaining type B after type A repair [14]. Further studies are necessary to better understand the predictive value of primary entry tear size and location.

The protective role of complete false lumen thrombosis is well established. However, a careful evaluation must be undertaken, as the presence of an ULP in the context of a thrombosed FL is associated with a higher risk class. About partial FL thrombosis, there are mixed results. Albeit the boundaries of “partial” thrombosis are by definition vague, being set in a different point of the range between 0 and 100% by the various authors, the explanation for the inconsistency of results may rely on a more specific reason, that is the concept of saccular FL formation. In a nutshell, it would not be the partial thrombosis itself that affects the evolution of the disease, but an anatomical configuration in which the blood enters the FL through the proximal ET, but does not find sufficient outflow channels, as the thrombosis have occluded them. This would lead to FL pressurization, increasing the risk of disease progression and complications.

According to this paradigm that ascribes to FL pressurization a central role in the development of adverse outcomes, we would expect that an increase in FL outflow channels causes the lowering of FL pressure and in turn predicts better outcomes. In fact, an increased number of tears predicted lower growth, [4, 25] and an increased estimated outflow was associated with a lower AE rate. [16] Nonetheless, the number of branch vessels involved, on one hand corresponds to outflow channels, but on the other hand may be related to increased risk of malperfusion, as pointed out by some studies in which it predicted adverse outcomes in the early stage.

About the FL longitudinal extent, solid evidences of its predictive value are still lacking.

Limitations

This review presents some limitations. First, the studies included populations that are not homogeneous. All of the studies included acute type B aortic dissections, but exclusion criteria varied. Some studies excluded patients affected by connective tissue disorders or IMH, while some did not. Some studies included only patients that were discharged without complications, while others also included initially

uncomplicated dissection patients that developed complications in the early stage, and others did not exclude dissections complicated at presentation. Moreover, even if all papers included patients who underwent imaging in the acute stage, the timeframe of inclusion varies between the first 24-48 hours from onset of symptoms to the first 14 days. As recently pointed out, aortic growth in dissection is not a linear phenomenon, since a rapid growth phase occurs in the first 25 days, followed by an intermediate one until 88 days and a plateau of slower growth thereafter. [50] This means that even a difference of few days in this stage may account for a substantial variability in aortic diameter, as some of the patients may have undergone the index imaging before the rapid growth, while others thereafter. It is still unclear the extent to which the rapid evolution phase may affect also other morphological predictors such as false lumen size, ET size and location and false lumen thrombosis.

Second, as previously stated, several inconsistencies existed regarding the definition of the predictors (e.g. FL thrombosis), limiting the comparability of results. Third, the definition of predicted outcomes also varied. For instance the threshold for aortic growth was set at different values. Moreover, some studies only included long term outcomes, others only early outcomes, and others both. Fourth, different statistical methods were used for prediction, with most studies using a multivariate analysis but some only univariate approach. Finally, the sample size varied, and many studies were probably underpowered for some combinations predictor-outcome.

CONCLUSION

Some of the traditional morphologic predictors in aortic dissection have proven to be consistent across the different studies and can be considered reliable. Others still present some limitation that could be overcome in the future thanks to technological advancements. Aortic size at presentation is a fairly consistent predictor of aortic growth and adverse events. FL size is suggestive of FL pressurization, but it is difficult to measure in a reproducible way, and a standard method is still lacking. The role of primary entry tear size and location is still partially unclear and further studies are necessary to better understand their predictive value. The protective role of complete false lumen thrombosis is well established. A saccular formation of the FL,

characterized by lack of outflow channels, could lead to FL pressurization, but further studies are necessary to clarify this mechanism.

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CHAPTER 2

Visceral ischemia complicating type B dissection: incidence, prognostic value, diagnosis and treatment

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INTRODUCTION

Organ malperfusion is a possible complication of Acute Type B aortic dissection (AD). Theoretically each branch arising from dissected aorta or downstream may be affected, resulting in end-organ ischemia. Obstruction of the celiac and/or mesenteric arteries may lead to visceral ischemia, wich is one of the most lethal complications of AD. A timely diagnosis and treatment are crucial to increase the chances of survival. Nowadays, the endovascular approach is the most frequently adopted in order to restore blood flow to the bowel, while open surgery is usually reserved for the cases of failure of endovascular treatment. In this chapter, the incidence, prognostic value, diagnosis and operative management of this dreaded complication of AD will be described.

INCIDENCE AND PROGNOSTIC VALUE

Two different mechanisms can lead to branch vessel obstruction: dynamic obstruction and static obstruction. The most common, occurring in about 80% of cases, is the dynamic obstruction.

The incidence of malperfusion syndrome in Acute Type B AD is about 20% [16], with mesenteric ischemia accounting for about one third of cases. Among complicated ATBAD, contemporary series report an incidence of visceral ischemia ranging from 14 to 25% [17]. Overall, in-hospital mortality directly realted to the visceral ischemia ranges from 2 to 11%. [17] In the IRAD registry, visceral ischemia of TBAD patients was 7%, and it heavily affected in hospital mortality, which was more than triplicated compared to patients without visceral ischemia (31% versus 9%). [1] In this cohort, patients with visceral ischemia were slightly but significantly younger than patients without visceral ischemia (59 vs 64 years), and often had malperfusion of other organs associated.

On average, Type B AD patients with visceral ischemia are younger than patients without visceral ischemia [1, 6].

In AD, malperfusion syndrome may become evident through onset of end-organ specific signs of ischemia. It is usually more severe in case of static malperfusion, while it may be intermittent and of varying intensity in case of dynamic obstruction. In

this case, care must be taken not to overlook the signs of ischemia, which can lead to a delay in diagnosis. Abdominal pain is present in the majority of cases of visceral ischemia. Nonetheless it is not an exclusive sign of malperfusion syndrome in AD, as it was reported to be present in 40% of patients without visceral ischemia. [1] Vomit, diarrea and bloody defecation are more specific but later signs. Malperfusion of visceral organs may be associated with malperfusion of other districts. Kidney malperfusion with acute renal failure was reported in 40% of cases with celiac-mesenteric ischmia, and only in 14% without. Femoral pulse deficit may be present, and a 28% rate of lower limb ischemia has been reported in patients with visceral malperfusion, while in patients without visceral malperfusion it was 13%. Also spinal chord ischemia has been reported more often in association with visceral malperfusion (5% versus 2%).

The suspicion of visceral malperfusion should increase in case of positivization of blood markers of ischemia. Levels of D-dimer, lactate, ammonia, transaminase, creatine phosphokinase, lactate and leukocytes may be elevated. Recently, other markers of mesenteric ischemia have been tested. The intestinal fatty acid-binding protein (I-FABP) was reported to have a sensitivity of 79% and a specificity of 91%. [18] However many markers of ischemia increase only after the intestine has become necrotic. Therefore, negative biochemical markers should not delay intervention if there is a strong suspicion of visceral malperfusion, such as in cases of acute abdomen. Imaging evidence of visceral malperfusion syndrome includes true lumen compression, branch vessel dissection and thrombosis, and reduced late-phase visceral enhancement on computed tomography angiography (CTA)

OPERATIVE MANAGEMENT

Thoracic endovascular aortic repair (TEVAR) is currently the first-line treatment in acute complicated Type B AD patients [7, 19].

The treatment consists in the coverage of the proximal entry tear in order to achieve expansion of the true lumen and decompression of false lumen. Thus, celiac or mesenteric artery obstruction are reversed in most cases. Otherwise, additional branch vessel stenting may be necessary in 0-20% of the cases [8-10]. TEVAR is therefore effective in treating mesenteric malperfusion in the setting of dynamic

obstruction [8]. However, in-hospital mortality rates are still considerable, ranging from 20 to 40% [9-11].

Furthermore, TEVAR-related complications may also occur in a small percentage of cases. Retrograde Type A AD and stent graft induced new entry tears have been described, in particular in relation to the use of stentgrafts provided of proximal bare spring, [20, 21] or in case of eccessive oversizing.[22] In order to prevent such complications, the stentgraft oversizing in Type B AD should not exceed 10%, and the proximal edge of the stentgraft should be deployed in a non-dissected zone. The use of a distal aortic bare metal stent in combination with the standard TEVAR (PETTICOAT – Provisional Extension To Induce Complete ATtachment – technique) [12] has been proposed both for the treatment of persistence of malperfusion after TEVAR and for the prevention of late complications. In the long run, complications may occur in patients treated with TEVAR, and in particular an aneurysmal evolution should be expected. In these cases, an endovascular treatment with branched stentgraft is feasible, but additional difficulties should be anticipated, especially if the visceral vessels origin from different lumina.[23, 24]

Endovascular fenestration of the dissection flap is a valid treatment option in case of persistence of false lumen pressurization and dynamic obstruction. It can be performed also as an alternative to TEVAR. If necessary, it can be accompanied by branch vessel stenting if static obstruction of a branch vessel is present.

A 17% early mortality rate was reported after endovascular fenestration in a cohort of 69 Type B AD patients with malperfusion performed in an experienced center. Mortality was due to aortic rupture in 7% of cases and malperfusion complications in 10% [13]. Following endovascular fenestration, even more than after TEVAR, the risk of late aortic dilatation should be taken into account. Freedom from aortic rupture or aortic repair rates at 1, 5, and 8 years of 80.2, 67.7 and 54.2% have been reported[13].

The technique of endovascular flap fenestration entails gaining access to both lumina as a first step. In this phase, intravascular or intraesophageal ultrasonoghraphy may be of great help to distinguish the two lumina and identify the tears. It also helps reduce the use of iodinated contrast medium, which is particularly important in case of renal malperfusion to lower the risk of renal failure. [12].

Pressure measurements allow to detect a pressure gradient between the two lumina, as well as between the proximal aorta and the branch vessels, providing an objective assessment of malperfusion. It is important do document the patency status of all branches before and after the procedure, as the resolution of obstruction in one branch vessel may lead to unpredictable changes in mobility of the dissection flap and potentially cause dynamic obstruction of other branch vessels.

If static obstruction of a branch vessel is found, this should be treated by stenting prior to the fenestration procedure. In order to perform fenestration, the dissection flap needs to be crossed through a re-entry tear, which are usually present at the level of branch vessels. Because the true lumen is smaller, it is usually easier to cross from the true lumen to the false lumen. If no re-entry tears are found, it is possible to pierce the dissection flap using a catheter and a stiff guidewire at the level of the obstructed artery. Then a guidewire is advanced through the fenestration and serial balloon angioplasty are performed until the pressure differential between the two lumina is abolished. If necessary, an uncovered stent may be placed in the true lumen to preserve patency of the fenestration. Other fenestration techniques have been described, such as the scissor technique and the cheese wire fenestration technique. In the latter, the guidewire, after crossing the septum is captured with a snare device and pulled out through the contralateral groin access. Then the guidewire is pulled inferiorly with a sawing motion to shear the dissection flap, stopping before the aortic bifurcation. However, pulling the flap downwards carries a risk of circumferential detachment of the intimal layer, which can result in aortic intussusception and obstruction. [12]

TEVAR is currently considered the first line treatment in most cases. [19] Fenestration may be more appropriate than TEVAR in patients with increased risk of spinal cord ischemia such as those with history of previous abdominal aortic repair, occlusion of hypogastric, subclavian or vertebral artery. On the contrary, TEVAR is particularly indicated in elderly patients, in case of aortic dilatation, and for intermediate-risk patietns (i.e. patients with refractory/recurrent pain or hypertension). Overall, the endovascular approach was used in almost 70% of patients with visceral ischemia enrolled in the IRAD in recent years [1]. In case of suspicion of intestinal infarction, an explorative laparoscopy or laparotomy is indicated. Acute abdomen, refractory lactic acidosis, or hemodynamic instability due

to ongoing intestinal malperfusion warrant immediate laparotomy and resection of necrotic intestinal tracts. (Fig. 18.6). A temporary closure technique such as Bogota bag or VAC closure system can be used to allow later inspection of the abdominal organs. In case endovascular techniques fail to restore vascularization to the visceral arteries, open surgery is necessary [1]. Surgical vascular reconstruction should also be considered in case of anatomical contraindication for TEVAR, such as unsuitable iliac accesses and insufficient proximal landing zones [7]. Furthermore, for patients with connective tissue disorders, TEVAR can be used as a bridge treatment, while open surgical aortic replacement is the treatment of choice. Open surgery should be considered also in younger patients, since long-term durability of TEVAR is still unclear.

Open surgical options to treat visceral malperfusion include open fenestration and aortic graft replacement.

Open fenestration requires exposure of the visceral segment of the aorta and clamping in supraceliac position A longitudinal aortotomy is then carried out on the left antero-lateral aortic wall and the dissection flap is widely resected to maximize the size of the single aortic lumen. The restoration of flow in the branch vessels may be assessed through intra-operative doppler-ultrasound.

Although open surgical fenestration appears to be effective at relieving malperfusion, it is still burdened by rates of in-hospital mortality of 20% [14]. There are concerns about late aneurysmal evolution after surgical fenestration, however positive results have been reported in this regard when reduction of aortic diameter to close the aortotomy was carried out. In fact, according to the law of Laplace, the tension on the aortic wall is proportional to the radius [14].

Graft replacement of thoracic or thoracoabdominal aorta is a more definitive option [1]. However, in the acute setting, in AD patients, it is associated with about 30% mortality [15] and a relevant risk of spinal cord ischemia in case of extensive distal thoracoabdominal resection [1].

Although the visceral malperfusion is an absolute indication for invasive treatment, the rate of patients with visceral ischemia who only receive medical management is around 20% in IRAD [1].

The reason for this discrepancy may be partially due to the precence in multicenter registries of patients with radiological or angiographic signs suggestive of mesenteric

obstruction without matching clinical signs [2]. More often, these patients are in such a poor clinical condition that are deemed unsuitable for endovascular or surgical intervention and an attempt of operative management is denied. In this class of patients the mortality rate reaches 50%. Indeed, in these patients the conservative treatment independently predicted in-hospital mortality [1]. Conversely, mortality rates after surgical and endovascular management of visceral ischemia were comparable (25.8% and 25.5%). However, the endovascular approach is considered the first line treatment [7, 19].

CONCLUSION

Visceral ischemia is a life-threatening complication of acute type B AD that mandates prompt intervention. Timeliness of diagnosis and treatment is crucial in order to successfully reverse end-organ ischemia. TEVAR is the first-line treatment. Endovascular fenestration can be used either as an alternative to TEVAR in selected patients or after TEVAR when it was not effective in restoring perfusion to the affected branch vessels. Open surgery should be limited to cases in which endovascular techniques are contraindicated or unsuccessful.

Another primary issue is the timeliness of diagnosis and subsequent reversal of end-organ ischemia.

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CHAPTER 3

Thoracic endovascular aortic repair versus best medical therapy in uncomplicated type B aortic dissection in the acute and subacute phase

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INTRODUCTION

Uncomplicated type B aortic dissection has been traditionally managed conservatively, with the aim to keep the hemodynamic under control until the stabilization of the aortic flap and the transition to the chronic phase. In the last years, thoracic endovascular aortic repair (TEVAR) has affirmed as the mainstay of treatment for complicated type B dissection, with good results compared to open surgery. More recently, TEVAR has been proposed and increasingly used also to treat uncomplicated dissection. In a recent survey, 37% of respondents affirmed to perform TEVAR in uncomplicated TBAD based on certain morphological criteria, while 8% affirmed to perform it routinely for uncomplicated cases[1]. Despite this increased popularity, strong evidence in favor of TEVAR for uncomplicated cases is still lacking. The INSTEAD trial failed to demonstrate a benefit in terms of mortality of TEVAR performed in subacute-chronic phase versus best medical therapy at two years[2]. The INSTEAD-XL demonstrated that the excess early mortality of TEVAR was largely due to peri-procedural risks, while TEVAR was advantageous concerning overall mortality, aorta-related mortality, aortic remodeling, and false lumen thrombosis at five years[3]. The ADSORB trial, in which patients in the acute phase were enrolled, showed a better outcome of TEVAR compared to BMT in terms of a composite outcome of incomplete false lumen thrombosis, aortic enlargement and rupture. However, it was underpowered for mortality[4].

The aim of this study was to analyze the outcomes of patients undergoing TEVAR in the acute and subacute phase versus BMT alone for uncomplicated TBAD in the IRAD registry. Moreover, we sought for any difference in terms of risk profile between patients selected for TEVAR and for BMT alone.

METHODS

Patient selection

The rationale and methods of IRAD have been previously described[5]. It is a multicenter retrospective observational registry encompassing 50 referral centers. In

the present study, patients with acute uncomplicated type B aortic dissection, enrolled in IRAD between January 1996 and July 2017 were included. Uncomplicated dissections were defined those that did not present at least one complication at presentation or during the hospital stay. Complications were the following: shock or hypotension, ischemic spinal cord damage, coma, periaortic hematoma, descending aortic diameter ≥ 5.5 cm, recurrent or refractory pain, refractory hypertension, limb ischemia, visceral ischemia, extension of dissection, aortic rupture, acute renal failure. Patients were divided into two groups according to whether or not they underwent TEVAR. The study was approved by the Institutional Review Committee at all participating IRAD institutions.

Data collection and analysis

Standardized data forms were used to collect the data. Collected clinical variables included patient demographics, history, clinical presentation, physical findings, imaging studies, management, and follow-up mortality. Yearly follow-up data were obtained up to 5 years after discharge. Data forms were entered into an online database maintained by the coordinating center at the University of Michigan, where they were reviewed for face validity and internal consistency. Data were reported as frequencies and percentages and as mean ±SD or median ±IQR as appropriate. Missing data were not defaulted to negative, and denominators reflect only reported cases.

RESULTS

Patients characteristics

At the time of data analysis, 2153 TBAD patients were enrolled in IRAD, of which 1127 were uncomplicated and were managed either medically (973) or with endovascular treatment (154). Among patients treated with endovascular treatment, 57 had no sufficient data to confirm that the treatment included a TEVAR and were therefore excluded resulting in 97 patients included in TEVAR group (group 2). Demographic and clinical history variables did not show any statistically significant difference between the BMT and TEVAR group, except for sex, with a higher prevalence of males among TEVAR patients (57.7% vs 77.3%, $p<0.001$), (table I).

Presenting symptoms were also comparable, with the exceptions of abrupt onset of pain, which was more prevalent in BMT patients (84.4% vs. 76.2%, p=0.05), (Table II). Regarding imaging findings, the mean ascending aortic diameter was slightly but significantly higher in the BMT group (3.8 vs 3.6 cm p=0.047). The status of the false lumen was significantly different in the two groups: Patent false lumen was more prevalent in the TEVAR group (49.1% vs75%, p=0.001), as well as partial thrombosis (33.3% vs 18.2%, p=0.039). Consistently, complete thrombosis was more prevalent in the BMT group, although the difference did not reach statistical significance (17% vs 6.8%, p=0.066). The distal extension of dissection into the abdominal aorta was also more present in the TEVAR group (44.4% vs 60.9%, p=0.009).

Endovascular treatment

The stentgraft deployment involved descending thoracic aorta in 87 cases (89.7%), aortic arch in 10 (10.3%), thoracoabdominal aorta in 17 (17.5%). Additionally, a flap fenestration was carried out in 2 cases (2.1%), an infrarenal stentgraft was deployed in 4 cases (4.1%), while celiac artery and renal artery were stented in 1 case each. Iliac artery stenting was carried out in 3 cases (3.1%). The stentgraft manufacturer was Medtronic in 18 cases (35.3%), Gore in 14 (27.5%), Cook in 16 (31.4%), other or not available in the remaining. The mean proximal diameter was 33.0±6.9, the mean distal diameter was 33.7±12.4 and the mean total graft length was 210±136.4.

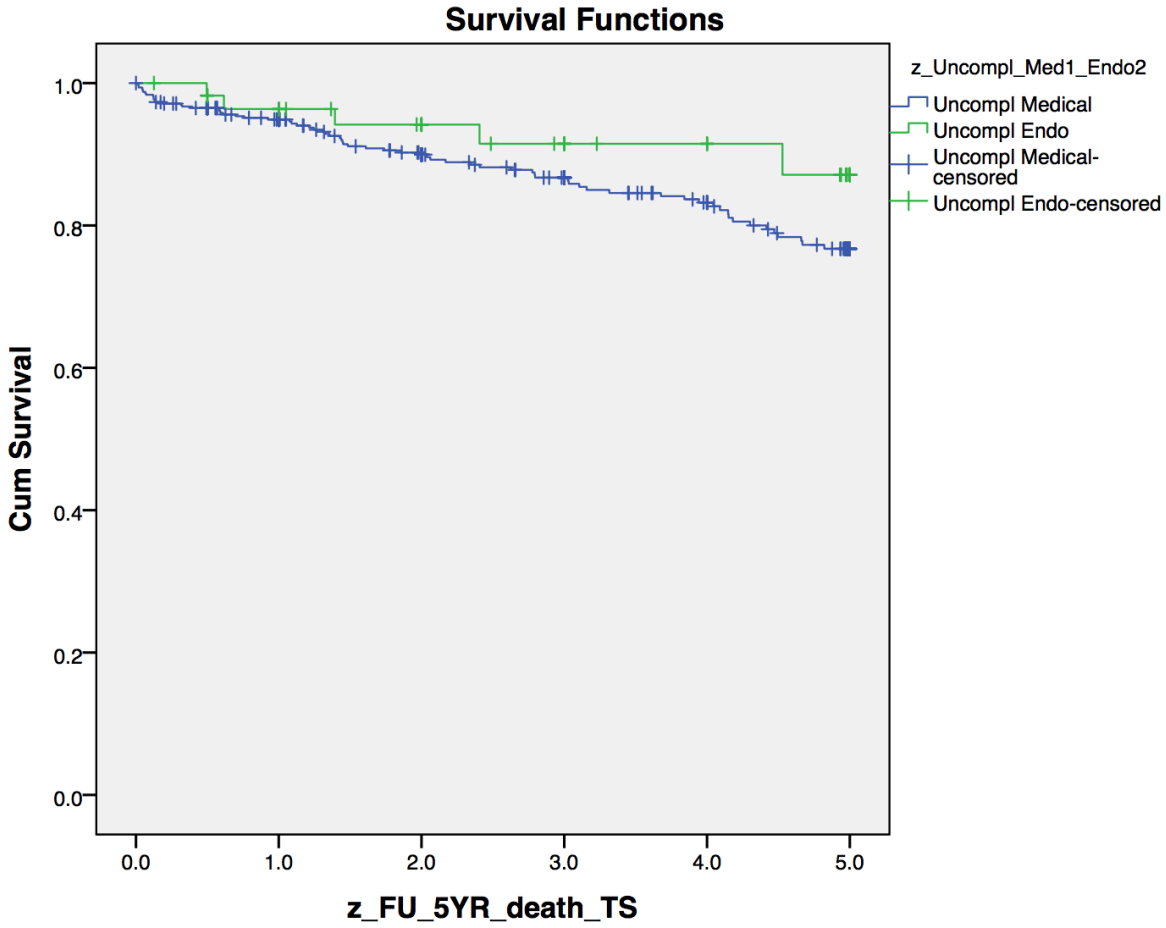
Medical therapy

Medica therapy administered initially and at discharge is reported in table XY. Regarding the initial therapy, there was a difference between the groups in the use of beta blocker (86.7% vs 78.3%, p=0.036), and vasodialtor (40.4% vs 22.2%, p=0.005). At discharge this difference was maintained (beta blocker, 93.6% vs 85.7%, p=0.004; vasodilator 26.9%14.8%, p=0.038), and there was a difference also in the use of calcium channel blocker (69.1% vs 50.6%, p=0.001) and anticoagulant (19.6% vs 56.7%, p<0.001).

Follow-up outcomes

The survival rates at 1, 3 and five years for the BMT and TEVAR groups were not significantly different (94.9±1.0 vs 97.1±2.8, 86.7±1.8 vs 88.7±6.3 and 76.7±2.7 vs

79.9±10 respectively). Freedom from new dissection or extension of dissection at two years was lower in the TEVAR group (91.1±1.7% vs 71.1±10.1%). No difference was found in terms of freedom from recurring symptoms or pain, aortic growth, aortic rupture, re-hospitalization, and late intervention.



DISCUSSION

The optimal treatment for uncomplicated acute type B aortic dissections is a matter of debate. traditionally, best medical therapy has been the mainstay of treatment for this class of patients. Nonetheless TEVAR, which is the first-line treatment for complicated cases, in the last years has been adopted as a possible option also for uncomplicated cases. Robust evidences in favor or against this approach are still lacking.

This study retrospectively analyzes a cohort of uncomplicated acute type B aortic dissection patients comparing those treated by BMT alone with those treated with BMT plus TEVAR. We found that patients undergoing TEVAR had more often a patency or a partial thrombosis of the false lumen compared to the BMT group. This finding is not surprising, as there are some evidences suggesting that the patency of the false lumen is associated with aortic-related mortality and adverse events,[6] and also that the partial thrombosis of the FL represents a class of increased risk.[7],[8] Therefore, the presence of this feature may have played a role in the decision to perform TEVAR.

Patients in the TEVAR group had also a higher rate of extension of dissection to the abdominal aorta. Although intuitively it might be thought that the larger extent of the dissection carries a higher risk of complications or evolution, evidence in this regard is limited[9],[10]. Thus it is not clear if this influenced the indication for treatment.

Regrding medical therapy at discharge, we found a higher rate of use of calcium-channel blocker in the BMT group. Actually, some previous study suggest a selective benefit of this drug class in acute type B aortic dissection treated medically, while its role after TEVAR is till unclear.[11],[12] Morover, it could be speculated that TEVAR resulted in an improved blood pressure control, requiring a lower number of anti-hypertensive drugs. Further studies are necessary to verify this hypothesis.

Interestingly, the prevalence of dissections extending to the aortic arch is not significantly different in the two groups. The fact that such dissections require a more technically demanding intervention including supra-aortic vessels rerouting and carry a higher risk of neurological complications might discourage from performing TEVAR in uncomplicated cases. Nonetheless, the extension to the aortic arch is considered

per se a risk factor for unfavorable evolution, prompting a more aggressive attitude.[13],[14] For this reason the optimal treatment for these patients is a matter of debate and the indication should relay on a careful balance of the risks that both therapeutic approach involve.

Another interesting finding of our study is the lower rate of freedom from extension of dissection or new dissections in the patients treated with TEVAR. The graft-related nature of this complications cannot be excluded. In fact the occurrence of retrograde dissections in patients undergoing TEVAR has been previously observed, in particular related with the use of stentgrafts with proximal bare spring,[15],[16] or excessive graft oversizing.[17] This finding is even more important, considering that extension of dissection was a predictor of 5-year mortality at Cox regression analysis in our study.

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CHAPTER 4

Results of TEVAR in complicated versus uncomplicated acute type B aortic dissection.

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INTRODUCTION

Classically, the indication for treatment of acute type B aortic dissection is based on the presence of complications, being best medical therapy the treatment of choice for uncomplicated cases. Recently, the endovascular treatment has been proposed as a viable alternative to BMT also for uncomplicated type B dissections, with the aim to prevent the development of future early and late complications. Nonetheless, this treatment is not without risks, especially when additional procedures involving supra-aortic vessels are required. The 2017 guidelines from the European Society for Vascular Surgery state that in uncomplicated acute type B aortic dissection early thoracic stent-grafting may be considered selectively. However, clear indications for treatment are still lacking, and the decision relies on a thorough evaluation of risks and benefits in the single cases. This study analyzes a cohort which is homogeneous as of stent graft type, allowing to compare outcomes overcoming the limitation of stent graft related variability. It also provides an insight on the real world usage of TEVAR in acute type B aortic dissections.

The aim of this study is to analyze the outcomes of TEVAR performed for complicated and uncomplicated acute type B aortic dissections in the W.L. Gore's Global Registry for Endovascular Aortic Treatment (GREAT) cohort.

METHODS

PATIENT COHORT

The GREAT is a prospective observational multicenter cohort registry that enrolled 5000 patients from November 2011 to November 2016, including patients undergoing implantation of abdominal and thoracic aortic stent graft from a single manufacturer. Patients from GREAT who underwent implantation of Gore® TAG® Thoracic Endoprosthesis (TAG) or Conformable Gore® TAG® Thoracic Endoprosthesis (CTAG) for acute type B aortic dissection were included in the study and data were retrospectively analyzed. The stent graft design and characteristics have been previously described. Inclusion criteria for GREAT were age 18 or older,

indication for aortic stent graft implantation as determined by the treating surgeon and acquisition of informed consent. Off-label use and non-standard indications did not represent exclusion criteria. All included patients provided written informed consent for their participation in the study. The trial was conducted in conformity with the Declaration of Helsinki and the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines, and was approved by the institutional review board of each participating center.

PROCEDURE

Each procedure was planned by sizing the stent graft based on aortic diameter and length. Per instruction for use (IFU), the proximal landing zone needs to be at least 20 mm long proximal to the primary entry tear, with the proximal extent in the non-dissected aorta. The diameter at proximal extent needs to be between 16 and 42 mm and an oversize of 10-20% relative to aortic inner diameter is recommended. When deemed necessary by the surgeon, additional proximal landing zone length was gained by covering the left subclavian artery, which revascularization through transposition or bypass was discretionary. The procedures were performed under general anesthesia. Cerebrospinal fluid drain, intraoperative trans-esophageal ultrasonography, heparin bolus and antibiotic prophylaxis were used according to the protocols of each center or at the discretion of the treating physicians. Surgical cut-down or percutaneous accesses were carried out based on the surgeon's preference. A completion angiogram was obtained at the end of every procedure. Technical success was defined as the deployment of the stent graft in the planned position with coverage of proximal entry tear and absence of type Ia endoleak, primary open conversion, and unintentional coverage of supraaortic or visceral vessels.

VARIABLES AND OUTCOMES

Collected variables included demographic details, cardiovascular risk factors, operative details, aortic related and unrelated adverse events, length of stay. Acute cases were defined as those whose time from symptom onset to diagnosis was14 days. Time from admission to intervention was recorded. Length of stent graft coverage was defined as the sum of the length of stent graft implanted. Patients

were divided into two groups based on the presence (group 1) or absence (group 2) of complications at presentation. Dissections presenting with rapid aortic expansion, aortic rupture and/or hypotension/shock, visceral, renal, or limb ischemia, paraplegia/ paraparesis, peri-aortic hematoma, recurrent or refractory pain, and refractory hypertension despite adequate medical therapy were defined as complicated. Primary outcomes were 30-day endoleak, stent graft migration, fracture or compression and aortic rupture. Reinterventions were defined as any invasive or minimally invasive measure related to the initial aortic procedure performed at any time following the initial procedure. Device related reinterventions included any measure related to a deficiency of the device implanted into the aorta. Follow-up controls and imaging tests were scheduled according to each centers' protocol. Date and cause of death were recorded. Data were collected on a web-based electronic database (iMedidata, Medidata Worldwide Solutions, Inc., New York, NY, USA) and reviewed by the Gore Clinical Research Department (W.L. Gore & Associates). Queries were posed to the investigators to address any issue regarding inconsistent or missing data. Monitoring site visits took place at the participating centers to audit the study documents for quality assessment, completeness and consistency with the electronic database.

STATISTICAL ANALYSIS

Statistical analysis was performed by the Gore Clinical Research Department. Continuous variables were reported as mean ± standard deviation or median with range. Categorical variables were reported as counts (percentage). Comparison between groups was performed with Fisher exact test for categorical variables and with Kruskal Wallis test for continuous variables. All data were analyzed using statistical SAS software (Copyright 2002-2008 by SAS Institute INC., Cary, NC, USA).

RESULTS

BASELINE DATA

Out of 5000 patients enrolled in the GREAT, 173 were treated by TEVAR for acute type B aortic dissection. Of these, 107 were complicated (group 1) and 66 were

uncomplicated (group 2). No statistically significant difference was present between the two groups in terms of demographics and comorbidities, except for cancer, which was more prevalent in the uncomplicated group (10.9% versus 2.9%, P=0.044).

OPERATIVE DATA

The avarage time from admission to treatment was 4.5±7.1 days (median=1, range 0-43 days) for group 1 and 3.5±5.5 days (median=1, range 0-26 days) for group 2 (P=.195). A percutaneous access was used in 40 cases (37.4%) in the complicated group versus 35 (53.0%) in uncomplicated group. The femoral artery was the access of choice in almost all cases, whereas an iliac access was used in one (0.9%) complicated case and two (3.0%) uncomplicated cases. Nevertheless a surgical conduit was necessary in five (4.7%) complicated cases and three (4.5%) uncomplicated cases. In two additional uncomplicated cases (3.0%) an endovascular conduit was performed. Additional nine (8.4%) and five (7.6%) brachial accesses and six (5.6%) and three (4.5%) other access sites were used in the complicated and uncomplicated groups respectively.

Procedures related to aortic branch vessels were 46 (43.0%) versus 14 (21.2%) in group 1 versus group 2 (P=.005). These procedures included coverage or embolization of the branch vessel in 22 (47.8%) versus six (42.9%) cases, surgical debranching in 24 (52.2%) versus six (42.9%) cases, stenting of branch vessel in eight (17.4%) versus three (21.4%) cases in group 1 versus group 2 respectively (all differences not significant). No chimney procedure was performed. In the subgroups of patients undergoing branch vessel procedures, the mean number of vessels involved was 1.4±0.75 (median 1, range1-4) versus 1.6±0.77 (median 1, range1-3). Left subclavian artery (LSA) was involved in 39 (84.8%) versus ten (71.4%) cases, and was surgically revascularized in twenty (51.3%) versus four (40.0%) cases and stented in four (10.3%) versus one (10.0%) cases in group 1 versus group 2 respectively. Other supra-aortic vessel surgical debranching included left common carotid artery (LCCA) in six (13.0%) versus three (21.4%) cases and innominate artery (IA) in two (4.3%) versus one (7.1%) cases. The remaining procedures on branch vessels were: for group 1, LCCA stenting in one case (2.2%), internal iliac artery embolization in one case (2.2%), other procedures in nine (19.6%) cases; for

group 2, celiac artery stenting in one case (7.1%), left renal artery stenting in one case (7.1%), other procedures in five (35.7%) cases.

The majority of patients in both group 1 and 2 had a CTAG stent graft implanted: 99 (92.5%) and 61 (92.4%), the remaining being TAG. Tapered stent graft were used in six (5.6%) and three (4.5%) for the two groups. The mean number of components for the two groups were 1.5+/-0.79 (median 1, range 1-5) and 1.7+/-0.77 (median 1.5, range 1-4). The mean total length of the stent graft implanted was 22.9 ± 10.1 cm (range, 10-55 cm) for group 1 and 25.5 ± 10.0 cm (10-60 cm) for group 2 (P=.106).

EARLY OUTCOMES

The mean length of stay was 14.4±10.47 (median 11, range 2-75) versus 9.8±7.83 (median 7.5, range 0-42) days in group 1 versus group 2 (p<.001). Thirty-day outcomes were not significantly different between the two groups. Total adverse events were nine (8.4%) and five (7.6%) in group 1 versus 2 respectively. Mortality was three (2.8%) versus one (1.5%) cases, stroke or TIA were two (1.9%) versus one (1.5%), paraplegia was one (0.9%) versus one (1.5%), reinterventions were eight (7.5%) versus two (3.0%). Only four of the interventions were device-related, all in group 1, including one open conversion and one additional stent graft. Four endoleaks occurred in group 1 (including one type Ia, one type Ib and one type III), whereas no endoleak was observed in group 2. One case of aortic rupture was observed in both groups (0.9% and 1.5%). No migrations or fractures were observed.

DISCUSSION

This study provides an overview of the real-world usage of Gore TAG and C-TAG stent graft in the treatment of acute complicated and uncomplicated type B aortic dissection. Early results show no significant difference in terms of mortality and new onset complications between the complicated and the initially uncomplicated groups. Thirty-day mortality and complication rates exceeding 10% and 20% respectively have been previously reported for complicated acute type B dissections treated by endovascular approach,. Indeed, the 30-day mortality and adverse event rate of

2.8% and 8.4% of the complicated group in the current series compare favorably with previously reported data.

In the uncomplicated group, 7.6% patients had adverse events including 1.5% mortality within 30 days. This rate is in line with reported data on uncomplicated acute type B aortic dissections treated with best medical therapy (BMT) alone or in combination with TEVAR, indicating mortality of 0-10%,,,. The result of the present study are consistent with a recently published retrospective study that reported early adverse event rate of 10.3% and mortality of 0.5% in patients treated by TEVAR for uncomplicated type B dissection. The same study reported similar early result for patients treated by BMT alone (mortality 2.6%, adverse events 4.5%).

Neurological complication rates in our series were overall good (stroke/TIA, 1.7%, SCI, 1.1%), and comparable to the ones reported in the literature (stroke/TIA, 2.3%, SCI, 1.3%). In the group of complicated dissections, stroke/TIAs were not higher, occurring in 1.9% and SCI in 0.9% cases. These rates may appear favorable if compared to those of a cohort of acute complicated type B dissections treated with a stent graft from another manufacturer (stroke/TIA, 8%, SCI, 2%). The similar rate of SCI is in line with the same median length of covered stent graft implanted between the complicated and uncomplicated groups. However, numbers are too small to draw any conclusion and are in line with results from metanalyses (stroke/TIA, 1.9-3.9%, SCI, 0.8-3.1%).

As reasonably expected, the length of stay reported in our study was significantly higher for the complicated group compared to the uncomplicated one. On the contrary, there was no significant difference between groups in the time from admission to intervention. The number of procedures related to aortic branch vessels, including coverage without revascularization, was also significantly higher in the complicated group. This finding may be due to the evaluation of the risk-benefit balance that was less favorable in the uncomplicated group when a debranching procedure was necessary. In other words, this finding may reflect a real-world preference of some treating physicians to avoid or at least limit the use of TEVAR in those uncomplicated cases that required additional procedures being technically more demanding and more invasive for the patient. This in in contrast with what reported in the ADSORB trial, where TEVAR procedures were performed according to randomization and the subclavian artery was covered in a much higher number of

cases (60%, all uncomplicated, compared to 15% of uncomplicated patients undergoing coverage of LSA in our study). Such difference might theoretically account for discrepancies in outcomes and should be considered in the future evaluation of follow-up data. Conversely, the decision whether to revascularize LSA in case of planned coverage was not statistically significant between complicated and uncomplicated dissections in our study, accounting in both cases for nearly half of the patients. This ratio is consistent with similar experiences,. Although the coverage of LSA without revascularization is considered a risk factor for neurological complications,, the decision whether to revascularize or not was at discretion of the surgeon, being mainly based on patient's anatomical features, such as dominant left vertebral artery or presence of left mammary to coronary bypass.

This study presents some limitations. Only early results are presented, making it impossible to draw any conclusion regarding mid and long term outcomes of TEVAR in acute dissection. Only patients undergoing TEVAR were enrolled, so a BMT group to compare the results of uncomplicated dissections lacks. Although the data were prospectively collected, they were analyzed retrospectively. Moreover, the results may be influenced by selection bias, given the observational nature of the study. Being it a multicenter registry, data may be heterogeneous as regards patient selection, procedural planning, anesthesiology management, surgical or hybrid room equipment, post-operative medication and follow-up protocols. Furthermore, the inclusion of off-label procedures may affect the reproducibility of results. The GREAT does not contemplate imaging data collection, so an analysis of outcomes in relation to morphologic features was not possible.

CONCLUSION

This retrospective analysis of the GREAT registry provides a picture of the real-world usage of TEVAR in the treatment of acute type B dissections. Comparing complicated versus uncomplicated cases, the hospital stay was longer for the first group, whereas perioperative complication and mortality rates were equally low for both. TEVAR entailing LSA coverage was less frequently performed for uncomplicated cases, likely because the treating surgeons weighed the potential benefits of the intervention against an increased invasiveness and risk, favoring BMT

in a larger number of uncomplicated cases. Further studies with a longer follow-up are necessary to better define the role of TEVAR in uncomplicated cases, in particular when LSA coverage is needed.

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CHAPTER 5

3D Printing of Aortic Models as a teaching tool for vascular surgery trainees

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INTRODUCTION

Background and rationale

In aortic disease management, thorough understanding of geometrical features is of primary importance. For instance the physician needs to visualize the exact length and angulation of aneurysm neck, the precise relations with branch arteries, the extension of false lumen and compression of true lumen in dissections.

For the medical student and the surgical trainee, it is counterintuitive to understand the implications of such concepts solely based on the traditional 2D imaging. Even if multiplanar reconstruction and volume rendering may be of some help, a comprehensive view of the disease is still hard to achieve.

Recent technological advancements have made it possible to produce patient-specific replicas of anatomical parts in a relatively time- and cost-effective manner. This technology has been used as a teaching tool in other fields of medicine, and its role in vascular surgery has to be better defined,.

Aim of the study

The aims of our study were to collect preliminary data on the use of 3D printing as a teaching tool for vascular surgery trainees and to validate a questionnaire addressing understanding of aortic disease in the educational setting.

MATERIALS AND METHODS

Study setting

This pilot study was conducted in the framework of University of Milan Medical School and Vascular Surgery Specialization School, under the coordination of the Thoracic Aortic Research Center, IRCCS Policlinico San Donato, Milano, Italy. Vascular Surgery trainees and other surgical trainees from all training years were proposed to take part in the study. The 3D model design and printing were carried out in collaboration with the Department of Civil Engineering and Architecture, University of Pavia, Italy,

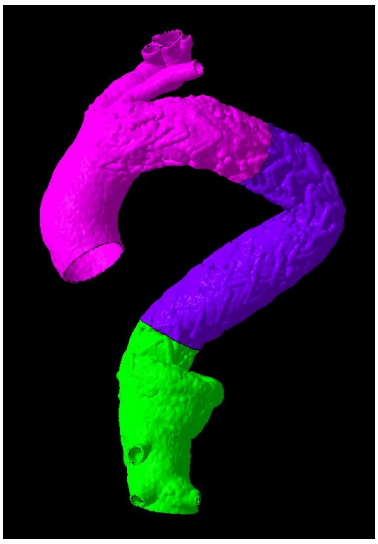
3D model manufacture

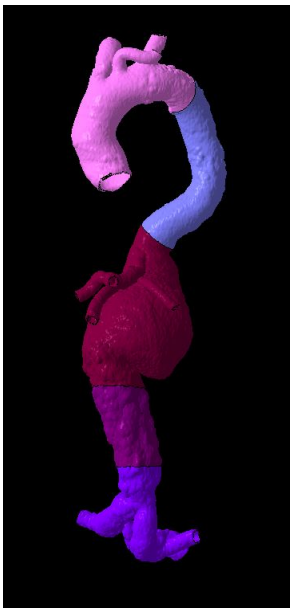
Ten models of aortic disease have been manufactured for this study starting from anonymized patients' CT-angiography imaging. The Image sections were reconstructed with isotropic voxels of 1.50 mm or less. Accurate region of interest (ROI) segmentation of the aortic lumen was carried out with a semiautomatic segmentation software (ITK-SNAP). The Digital Imaging and Communications in Medicine (DICOM) data were imported into the ITK-SNAP software for image processing. Presegmentation consisted in applying a two-sided (lower and upper value) threshold gray scale interval in order to obtain a mask based on voxel density corresponding to aortic lumen. Region growing of aortic lumen was then performed using an active contour evolution automated algorithm. In order to standardize the procedure, the initialization is carried out by putting seven seed points in a standard manner, according to a previously published protocol. The segmented regions were carefully reviewed against source imaging for accuracy and manual segmentation tools were used to draw or erase voxels accordingly. A standard stereolithography solid-to-layer format (STL) file were generated from segmented volume. The 3-Matic software (Materialise, Ann Arbor, Mich) was used to edit the STL file so as to cut the closed surface open at the extremities and add a 1,5 mm thickness with a hollowing function. The virtual models were cut at the level of the intended proximal landing zone and a junction mechanism was designed such to obtain a disassembling model.

The models were printed with the vat photopolymerization technique, in a transparent rigid resin. Postprocessing included solvent rinse, smoothing of step edges by UV light sanding and application of a UV-resistant sealant, in order to yield nearly water-clear appearance.

Model demostration

The models were displayed to the trainees, including a model in which a stent graft had been previously deployed inside, so as to simulate the intervention. The models were detachable in order to allow visual and tactile exploration of the proximal landing zone.





Variables and outcome measure

A questionnaires was developed to measure the improvement in understanding from before to after the 3D printed model demonstration.Measured variables included demographics (age, gender) and year of training.

Sample size

As this is a pilot study, the minimum sample size has been calculated considering three subjects per item of the questionnaire. The questionnaire consisted of ten items. Therefore, the minimum sample size was 30 trainees.

Statistical analysis

All variables were reported using descriptive statistics. Categorical data were reported as counts (percentage); continuous data were reported as means +/- standard deviation (M +/- SD) for normally distributed variables, and as median (interquartile range) for continuous data non-normally distributed. The study of skewness and kurtosis were used to preliminarily assess the normal distribution of the variables, followed by the Kolmogorov–Smirnov test. Outcomes measured with VAS were considered as continuous variables ranging from 0 to 100. Outcomes before and after the 3D printed model presentation were compared with Wilcoxon matched-pairs signed-ranks test. The missing data were managed by using a pairwise approach.

Statistical analysis was performed with SPSS version 22, setting the level of significance of each test at 0,05 and two-tailed.

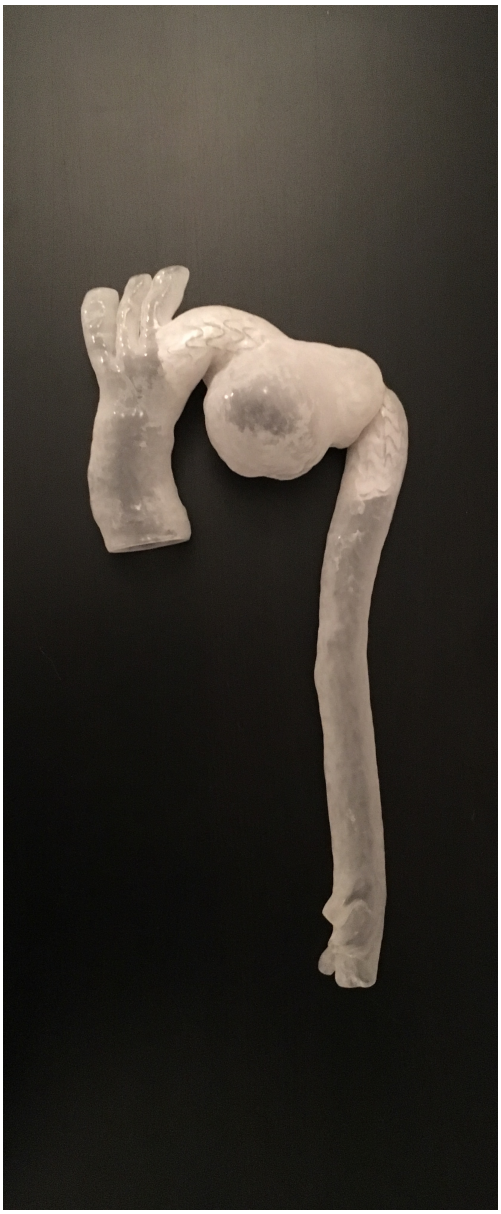
Questionnaire validation

Face and content validity were tested through content validity index and open-ended questions on clarity and pertinence of the items. Content validity was determined using the viewpoints of a panel of experts. Their evaluation was firstly based on a three-point Likert scale (1= not necessary; 2= useful but not essential; 3 = essential) to compute the content validity ratio (CVR). Its formula is CVR=(Ne - N/2)/(N/2), in which the Ne is the number of raters indicating "essential" and N is the total number of raters. CVR could vary between +1 and -1, with higher scores indicating greater agreement among raters on the necessity to keep the evaluated item in the scale. Secondly, the panel of experts in vascular surgery (i.e. panelists) were asked to rate questionnaire items in terms of their relevancy to the construct underlying the scale using a four-point ordinal scale (1 = not relevant; 2 = somewhat relevant; 3 = quite relevant; 4 = highly relevant). CVI was calculated both for the items level (I-CVIs) and for the scale-level (S-CVI). To obtain the relevancy of each item (I-CVIs), the number of experts judging the item as relevant (i.e. ratings ≥ 3) was divided by the total number of panelists. Thus, I-CVIs was computed as the number of experts giving a rating 3 or 4 to the relevancy of each item, divided by the total number of the panelists, expressing the proportion of agreement on the relevancy of each item, where the index could

range between zero and one. Furthermore, S-CVI will be defined as the proportion of total items judged as having content validity, and it will be computed as the average of the I-CVIs.

To obtain face validity, the investigators asked to the same panel of experts to answer to three open-ended questions, transcribed verbatim. The questions were aimed to explore the difficulty level of the items' wording, the desired relationship between items and the main objective of the questionnaire, and eventually to discuss about ambiguity and misinterpretations of items. All the answers were analyzed using a narrative analysis to summarize the main emerging themes.

Construct validity was assessed through Explorative Factorial Analysis (EFA) to assess the latent structure of the questionnaire (i.e. psychometric questionnaire' properties). The factoriability assumptions have been verified through Bartlett's sphericity test and Keiser-Meyer-Olkin index prior to EFA. The number of factors to be extracted in the EFA was defined using the following: chi-square (X2), the root mean square error of approximation (RMSEA); the comparative fit index (CFI) as indices of goodness of fit; the theoretical meaning of the factors; the Scree test interpretation. Internal consistency was assessed through Cronbach's alpha. Test-retest method was used to assess stability.



RESULTS

Six models were 3D printed, representing one aneurysm of the aortic arch, one aneurysm of proximal descending aorta, one DeBackey type IIIb aortic dissection with chronic aneurysmal evolution, one Crawford type II thoracoabdominal aneurysm with hemiarch replacement and extreme arch tortuosity, one Crawford type IV thoracoabdominal aneurysm and one type Ib endoleak after TEVAR.

A panel of 15 experts (four expert in method, 11 vascular surgeons) participated in evaluating face and content validity of the questionnaire. The ten items of the questionnaire were relevant and appropriate (CVR between 0.6 and 1.0, median 0.9; S-CVI = 0.99). The narrative analysis of the comments has highlighted the overall clarity of the items.

Twenty-five residents took part in the study. The Bartlett test of sphericity was significant (for T0: X^2 = 185,70; *d.f.* = 45; *P*-value <0.001; for T1: X^2 = 282.04; *d.f.* = 45; *P*-value <0.001) and the Kaiser–Meyer–Olkin (KMO) test was 0.82 for T0 and 0.80 for T1. Therefore, the correlation matrix was considered suitable for factor analysis. The study of the eigenvalues, the scree test and the semantic interpretation of the items suggested the extraction of one dimension.

Factor loadings are shown in table

The PCA model using one factor solution explained 58.92 of the total variance at T0 and 65.16% at T1.

The study of the internal consistency was good (α Cronbach = 0.92 at T0; 0.94 at T1).

Skewness was -0.981 (standard error [SE]=464) at T0 and -0.861 (SE=464) at T1. Kurtosis was 1.167 (SE=902) at T0 and 1.292 (SE=902) at T1. The median (interquartile range) was 7.3 (1.71) at T0 and 7.6 (1.15) at T1.

The change in understanding was positive in 17 cases (mean 12.09, sum 205.5), negative in five (mean 9.5, sum 47.5) and nil in three.

The understanding improved significantly from T0 to T1 (Z, -2.568, P=0.010)

The study of correlation revealed that although at T0 the understanding does not differ according to the year of specialization, at T1 there is a correlation between year of specialization and understanding. Post-hoc analysis on stratified groups

suggested a better improvement of understanding from second year of specialization on, but did not reach statistical significance.

DISCUSSION

Three-D printing is a novel technology that is gaining a growing interest in the medical scientific community.

Its use with educational purposes has been reported in different medical and surgical specialties. Our study proved the feasibility of using 3D printed patient-derived aortic disease models to improve the learning experience of surgical trainees. The models were used in the context of a seminar on the treatment and complications of aortic disease. At the end of the seminar the surgical trainees were asked to answer the questionnaire about perceived understanding of specific issues. Thereafter they were given the 3D printed models and could spend some time manipulating and disassembling the models, having the chance to thoroughly understand the tridimensional morphology. Then, they were asked to answer the questionnaire a second time. There was a significant increase of perceived understanding overall and for each item of the questionnaire. A similar experience was reported by Biglino et al, who used 3D printed heart models as a teaching tool during a specialized course for cardiac nurses. The heart models represented congenital heart disease after repair[1]. In both cases, the visualization of a complex tridimensional morphology is essential to understand the disease and its implications. Actually, the combination the different sensory inputs of touch and binocular vision is thought to improve the spatial conceptualization and understanding of complex anatomy, as underlined by Matsumoto et al, who reported the Mayo Clinic experience of 3DP as an imaging tool. Traditionally, the teaching of anatomy and pathology relied on wet cadaveric material and, more recently, plastinated prosections. However, cadaveric material for teaching purposes is hardly available nowadays in some geographical areas, including the country where our study was conducted. Moreover, the tridimensional shape of the aorta is maintained by the blood pressure, and is lost after death. Conversely, 3DP reproduces the aortic shape as it is in vivo. The teaching value of 3D printing

is not limited to seminars and courses, as it can be used also to discuss the patient-specific pre-procedural planning, and help to visualize tridimensional morphology during fluoroscopy. Wilasrusmee et al demonstrated that trainee's ability to understand spatial features of aortic aneurysm and make a correct decision on anatomical suitability for endovascular treatment is generally lacking, but can improve after the use of 3D printed models. Interestingly, a study of Tam et al demonstrated that when used for challenging cases 3DP models can improve confidence of planning and even result in a change of strategy not only for trainees, but also for experienced operators. In fact 3DP has been recently proposed as a tool to assist the planning of complex endovascular procedures, including using it as a guide for back table stent graft modification. However, the education of surgical trainees remains the field where the room for improvement is bigger. It has been demonstrated that trainee participation in aneurysm repair, although not associated with major adverse perioperative outcomes, is associated with an increased operative time and length of stay, which in turn results in increased costs. Training with a 3DP-based patient-specific simulation has already proven to reduce operative time and costs. Nonetheless, the use of 3DP in surgical education is still in its infancy and its costs are relatively high. Multi-material colored models have been used for the study and planning of arch replacement procedures. The multi-material 3DP technique permits also the reproduction of large tumors involving great vessels, that can be a valuable adjunct for the procedure planning. Recently developed 3D printable metamaterials will give the possibility to produce more and more realistic patient-specific models that can be used for simulations. It has been proposed that simulations become part of the standard training curricula and practical examination of surgical trainees. Indeed, 3DP models have been already used for case-specific simulations of robotic surgery to treat visceral vessels aneurysms. Itagaki et al reported the use of a 3DP models to simulate the endovascular treatment of visceral vessels aneurysms, permitting to test different catheters and guidewires and select the ones that performed better. Similar approaches have been used in the simulation of intracranial aneurysm treatment both with endovascular approach and with open surgery,,. Moreover, patient-specific simulations of transcatheter aortic valve implantation have been carried out by

many authors.,,,. 3DP will likely become an essential adjunct in the learning experience of surgical trainees also in other scenarios.

Limitations

This is a pilot study and its primary aims are to collect preliminary data and to validate a questionnaire. Therefore, data on the improvement of understanding are limited due to the design of the study. A paired approach was used to evaluate the change of perceived understanding before and after the demonstration of the 3DP models. Only a subjective evaluation of understanding was contemplated, while an objective measurement is lacking. We asked the participants to answer the questions as honestly as possible, and the questionnaire forms were anonymous. Nonetheless, social desirability bias may theoretically affect the results. A randomized controlled trial with a larger sample size is necessary to verify the hypothesis that 3DP improve understanding in this setting. Moreover, the models used for this study were 3D printed in a rigid transparent resin. More realistic flexible models will be likely available at a reasonable cost in the future.

CONCLUSION

The use of 3D printed patient-specific aortic models for the education of surgical trainees is feasible. Preliminary data suggest that the demonstration of the models significantly improved the understanding of aortic disease treatment and complications. A randomized controlled trial is necessary to confirm this finding.

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CHAPTER 6

Future perspectives

The latest technological advancement is opening new frontiers in the study of morphological and functional features as predictors of adverse outcomes in type B aortic dissection. The center-lumen-line (CLL) reconstruction, which is possible to obtain through dedicated softwares, improved considerably the accuracy of aortic measurements. Based on this method, novel parameters can be investigated, such as angulation and lengths between different anatomical landmarks and pathological features. [1,2] For instance, the position of intimal tears, ulcer-like projections (ULP), site of maximum enlargement or maximum true lumen compression can be accurately localized along the CLL, and recorded on a multi-dimensional aortic map. The representation of data based on a CLL-based aortic map will allow to approach the problem of outcome prediction with innovative computational techniques, such as machine learning algorithms. A further impulse towards the understanding of predictive features will be given by new imaging and computational approaches. On one hand, the development of more and more accurate computational fluid dynamics (CFD) models will allow to estimate wall shear stress and other forces acting on the vessel wall, [3,4] on the other hand, the 4D flow MRI will potentially show patterns of flow and movement of the dissection flap associated with worse outcome.[5] In fact, it is reasonably conceivable that the false lumen (FL) pressurization arises from a dynamic interaction between flow characteristics and flap movements that may lead to a valve-like mechanism, with different grades of severity depending on morphology-specific cutoff values of systolic output, frequency, and peripheral resistance. For instance, morphological features such as ULP and saccular FL formation, might be associated with particular patterns of flow and flap movement, each of which might show different predictive value.

Another promising technique is the positron-emission tomography/computed tomography (PET/CT), that has already revealed increased metabolic activity in

aortic dissections with higher remodeling and clinical evolution in the chronic phase. [6]

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