Aortic growth and development of partial false lumen thrombosis are associated with late adverse events in type B aortic dissection

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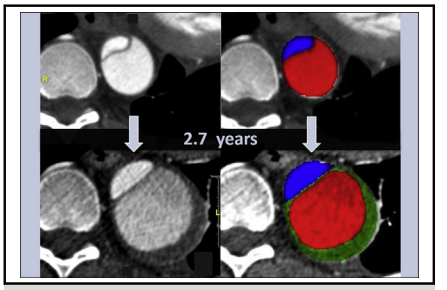
ABSTRACT

Background: Patients with medically treated type B aortic dissection (TBAD) remain at significant risk for late adverse events (LAEs). We hypothesize that not only initial morphological features, but also their change over time at follow-up are associated with LAEs.

Materials and Methods: Baseline and 188 follow-up computed tomography (CT) scans with a median follow-up time of 4 years (range, 10 days to 12.7 years) of 47 patients with acute uncomplicated TBAD were retrospectively reviewed. Morphological features (n = 8) were quantified at baseline and each follow-up. Medical records were reviewed for LAEs, which were defined according to current guidelines. To assess the effects of changes of morphological features over time, the linear mixed effects models were combined with Cox proportional hazards regression for the time-to-event outcome using a joint modeling approach.

Results: LAEs occurred in 21 of 47 patients at a median of 6.6 years (95% confidence interval [CI], 5.1-11.2 years). Among the 8 investigated morphological features, the following 3 features showed strong association with LAEs: increase in partial false lumen thrombosis area (hazard ratio [HR], 1.39; 95% CI, 1.18-1.66 per cm^2 increase; $P < .001$), increase of major aortic diameter (HR, 1.24; 95% CI, 1.13-1.37 per mm increase; $P < .001$), and increase in the circumferential extent of false lumen (HR, 1.05; 95% CI, 1.01-1.10 per degree increase; $P < .001$).

Conclusions: In medically treated TBAD, increases in aortic diameter, new or increased partial false lumen thrombosis area, and increases of circumferential extent of the false lumen are strongly associated with LAEs. (J Thorac Cardiovasc Surg 2021;161:1184-90)



Native and segmented computed tomography images showing new thrombus (*green*) in a growing false lumen (*red*).

CENTRAL MESSAGE

An increase in maximum diameter and increased or new partial false lumen thrombosis are associated with late adverse events in uncomplicated type B aortic dissections.

PERSPECTIVE

Morphological features extracted from imaging data may improve risk stratification in patients with initially uncomplicated type B aortic dissection. We demonstrate that aortic growth and the increase in or new development of false lumen thrombus are associated with late adverse events, suggesting that follow-up imaging data should be included in future risk prediction models.

See Commentaries on pages 1191 and 1192.

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Received for publication Nov 4, 2018; revisions received Sept 13, 2019; accepted for publication Oct 2, 2019; available ahead of print Oct 31, 2019.

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0022-5223/$36.00

https://doi.org/10.1016/j.jtcvs.2019.10.074

Abbreviations and Acronyms

CI = confidence interval
CT = computed tomography
FDA = Food and Drug Administration
HR = hazard ratio
IQR = interquartile range
LAE = late adverse event
TBAD = type B aortic dissection
TEVAR = thoracic endovascular aortic repair

Scanning this QR code will take you to the table of contents to access supplementary information.

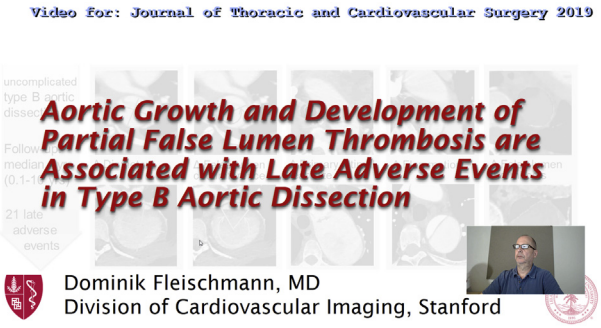
Although thoracic endovascular aortic repair (TEVAR) has recently become a Food and Drug Administration (FDA)-approved alternative to medical management in patients with acute uncomplicated type B aortic dissection (TBAD), it is becoming increasingly clear that only a subset of high-risk patients may benefit from the favorable effects of early TEVAR on aortic remodeling.[1] For patients with a low likelihood of developing late complications, the small but potentially devastating procedural risks of TEVAR, such as stroke, paraplegia, or retrograde type A dissection, might not be warranted.[2,3] Risk stratification is thus highly desirable in this population and several groups have suggested the use of morphologic parameters extracted from imaging data to guide therapy.[4-7]

Because morphological parameters can change over time, an important prerequisite for any clinically useful risk prediction model for patients with uncomplicated TBAD is the ability to capture the evolution of these morphological features over time and, if necessary, update an initial risk estimate with information obtained at each follow-up.[8] However, the evolution of morphological risk factors over time and the implication for future risk in patients with initially uncomplicated TBAD is currently unknown, with the exception of aortic diameter, which can also assume the role of an outcome variable in the form of a predefined size threshold for intervention.[8]

The purpose of this study was to investigate whether currently known or presumed morphological risk factors change over time on serial imaging, and whether such changes are independently associated with the risk for future events in patients with initially uncomplicated TBAD (Video 1).

METHODS

This study was approved by our Institutional Review Board. The requirement for written informed consent was waived owing to the retrospective nature of this investigation.



VIDEO 1. Video (12 minutes) of a slide presentation by the senior author of the study, explaining the motivation and conclusions of this paper. Video available at: https://www.jtcvs.org/article/S0022-5223(19)32372-4/fulltext.

Subjects

Patients were selected from an existing cohort of retrospectively identified patients presenting with acute, uncomplicated TBAD between January 2003 and 2012[5,8] (Figure 1). Patients with intramural hematoma were excluded. For the purposes of this investigation and due to the time-consuming manual processing of serial, high-resolution imaging datasets, we restricted our analysis to the subjects of 1 of the participating aortic centers with follow-up until April 2017. Patients were included if they survived the index hospitalization under medical management without the development of acute complications within 30 days, including death, aortic rupture, or signs of impending rupture, organ or limb ischemia, and uncontrollable pain or hypertension, and if at least 1 follow-up imaging study was available. Patient demographics, clinical characteristics (including a history of hypertension, diabetes mellitus, or smoking), clinical course, and interventions were retrieved from the electronic medical record (Table 1). Late adverse events (LAEs) were defined as any of the following, occurring at least 30 days after the initial event: aneurysmal degeneration of the aorta (defined as maximum aortic diameter of >6 cm), rapid growth of >0.5 cm in a 6-month period, new dissection, rupture, malperfusion, or death. Patients were followed until the occurrence of an LAE, an intervention, or the last available encounter on record.

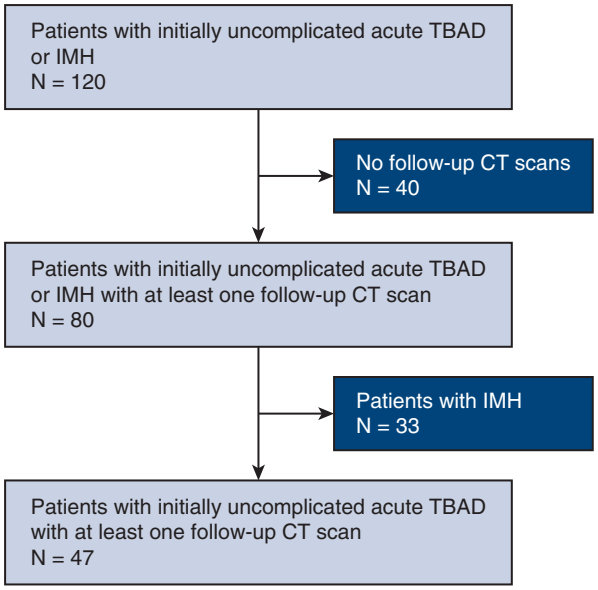


FIGURE 1. CONSORT diagram of the study population. *TBAD*, Type B aortic dissection; *IMH*, intramural hematoma; *CT*, computed tomography.

TABLE 1. Patient characteristics

Characteristic	Value
Total number	47
Age, y, median (IQR)	50 (37-59.5)
Male sex, n (%)	31 (66)
Hypertension, n (%)	43 (91)
Hyperlipidemia, n (%)	14 (30)
Diabetes mellitus, n (%)	5 (11)
Smoking, n (%)*	21 (45)
Connective tissue disease, n (%)	12 (26)
Number of events, n (%)	21 (45)
Median time to event, n (%)	NA
Follow-ups, n, median (IQR)	4 (2-5)
Follow-up, d/y, median (IQR)	1449 (438-2158)/4.0 (1.3-5.9)

IQR, Interquartile range; *NA*, not applicable. *Active or former smoker.

Imaging Data

All imaging datasets were obtained with state-of-the-art multiple-detector row computed tomography (CT) equipment (8 or more detector rows), with 0.75- to 1.25-mm-thick sections reconstructed at 1-mm or smaller intervals. All baseline and follow-up CT scans were analyzed using dedicated 3-dimensional image postprocessing software (Aquarius iNtuition version 4.4.12; TeraRecon, Foster City, Calif), which allows simultaneous review of spatially matched serial datasets. Morphological features were reviewed and measured by 2 cardiovascular radiologists at baseline and at every follow-up imaging, which typically occurred at 3, 6, and 12 months and yearly thereafter, although the intervals could vary between patients.

Serial Assessment of Morphological Features

In addition to 4 baseline anatomic features (a-d) that have recently been associated with LAEs in a cohort that included the current study population,[5] we also included several other plausible morphological predictors of LAEs (e-h) from the literature[4,9,10] to investigate whether, and if so to what extent, any of these features changed over time, and whether those changes were predictive of LAEs:

(a) The maximum aortic diameter was defined as the greater of 2 orthogonal diameters (major and minor axes) obtained in a cross-sectional plane perpendicular to the aortic centerline and measured using electronic calipers. To determine aortic growth, and because growth occurred consistently at the location of maximum diameter, the location of the maximum aortic diameter as determined on the last available CT scan was propagated to all previous scans of the same patient.

(b) To capture the size of the false lumen, independent of the movement of the dissection flap over the cardiac cycle, we used an electronic protractor to measure the circumferential extent of the true and false lumens in angular degrees along the outer aortic wall as described previously.[5] These measurements were performed at the level of maximum aortic diameter at each time point.

(c) The total number of visible intercostal arteries and their respective origins off the true lumen versus the false lumen were counted and recorded based on transverse source images on each scan.

(d) The aortic false lumen drainage pattern was estimated by visually assessing whether the origins of the left subclavian, visceral, renal, and iliac arteries arose off the true, the false, or both lumina, respectively, on each scan. Increased false lumen drainage has been shown to reduce the risk of LAEs.

(e) The size of the primary intimal tear was measured using electronic calipers in 2 dimensions (transverse and craniocaudal) using transverse images with sagittal and coronal reformations of each scan.

(f) The number of secondary/reentry tears were counted on transverse source images and noted on each scan.

(g) The longitudinal extent (thoracic and/or abdominal), thickness, and mobility of the dissection flap were assessed on transverse images at the level of the celiac artery. The thickness of the dissection membrane was measured using electronic calipers. The dissection flap was defined as mobile if typical motion artifacts, such as a double contour of the flap, were visible; otherwise, the flap was considered stiff.

(h) In an attempt to capture and quantify the presence and changes of partial false lumen thrombus—defined as the presence of a low-attenuated, nonenhancing filling defect within the contrast-opacified false lumen—we first used a 6-point visual grading system to semiquantitatively describe the proportion of thrombosed versus nonthrombosed false lumen: 1 = 0% (no thrombus); 2 = 1% to 24%; 3 = 25% to 50%; 4 = 51% to 75%; 5 = 76% to 99%; 6 = 100% (completely thrombosed). We also measured the cross-sectional area of false lumen thrombus, as well as corresponding true and false lumen areas, at the level of maximum false lumen thrombus area in each scan (Figure 2).

Statistical Analysis

Statistical analyses were performed using R version 3.3.3. (R Foundation for Statistical Computing, Vienna, Austria). Patient characteristics are given as median and interquartile range (IQR), or as count and percentage. Median LAE-free survival was quantified using the Kaplan-Meier method.

We used a stepwise analytic approach to jointly model the longitudinal data (ie, changes in morphological features over time), with time-to-event outcomes.[11] First, we used mixed-effects regression to assess changes in each predictor variable (ie, the morphological feature) over time. Each mixed-effects model included a random intercept and random slope, to account for the clustering of multiple measurements per patient over time. We allowed linear and quadratic terms for time and used the Akaike information criterion to determine the best-fitting model by choosing the model with the lowest Akaike information criterion value.

We next assessed the effects of longitudinal changes in predictor variables on time-to-event outcomes, by joining the mixed-effects models with Cox proportional hazards regression. Initially, the association for each morphological feature was assessed separately. For the multivariable models, each significant association was subsequently corrected by adding covariates to the Cox proportional hazards submodel. As covariates, we considered baseline values of all other significant features, as well as the presence of connective tissue disease.

RESULTS

We identified a total of 47 patients. In 21 patients, an LAE occurred over the course of follow-up. Patient demographics and clinical characteristics are given in Table 1. A total of 235 CT scans (47 baseline and 188 follow-up) were analyzed. The median duration of follow-up was 4.0 years (range, 10 days to 12.7 years). The median time to an LAE was 6.6 years (95% confidence interval [CI], 5.1-11.2) years. A Kaplan-Meier curve showing the probability of being LAE-free over the course of follow-up for the entire cohort is shown in Figure 3. The shaded area denotes the confidence bound around the Kaplan-Meier estimates. Events were driven predominantly by chronic aneurysm formation, occurring in 18 of 21 patients (86%). One patient demonstrated rapid aortic growth, and 1 patient developed acute limb ischemia within the first year. One of 21 patients (5%) developed a new type A dissection at 8 years after the initial event. LAEs were treated surgically in 14 patients, using endovascular repair in 5, and 2 patients were managed medically.

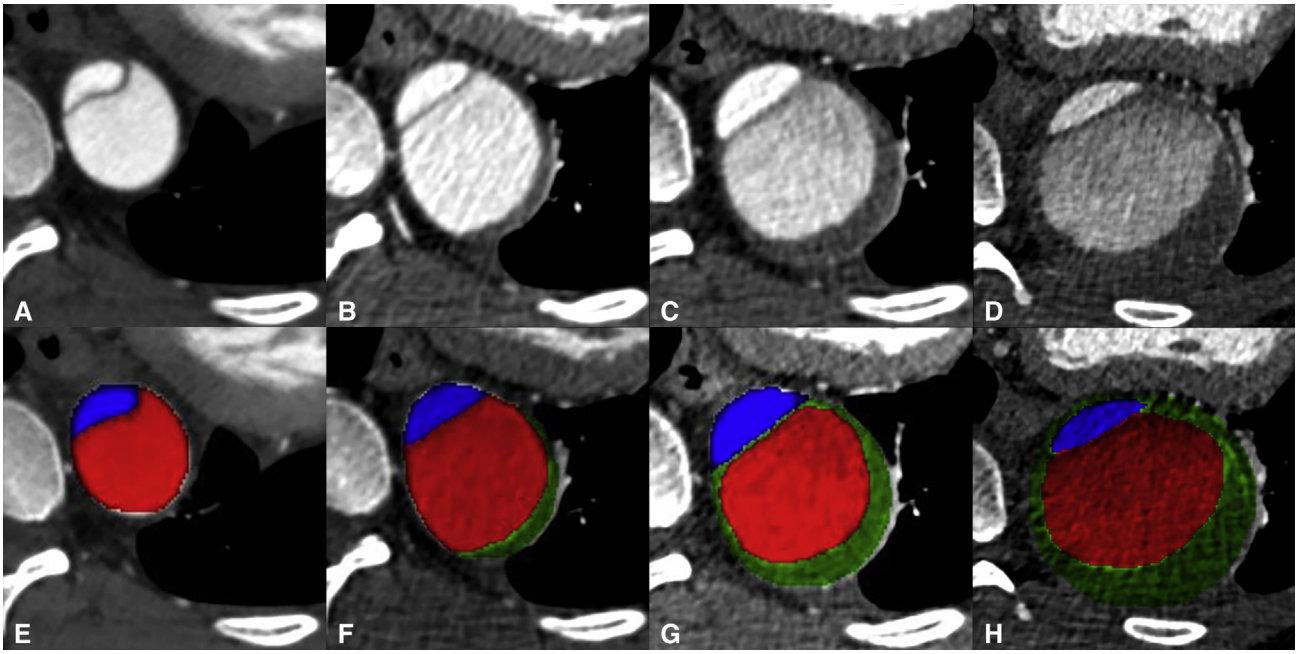


FIGURE 2. Imaging example of area measurement of true lumen, false lumen, and false lumen thrombosis. Cross-sectional images at baseline (A) and follow-up at 7 months (B), 2 years (C), and after 4 years (D). Corresponding baseline (E) and follow-up (F-H) images with color coding of measured areas for the true lumen (*blue*), false lumen (*red*), and thrombus within the false lumen (*green*, in F-H).

Stable Morphological Features Over Time

Several key features of aortic dissection were remarkably stable over time without any noticeable or quantifiable changes compared with baseline and thus were not included in the analyses: proximal and distal extent of the false lumen, location of the primary intimal tear, and large branch vessel blood supply from the true lumen versus the false lumen. This observation confirms that the longitudinal and circumferential boundaries of the false lumen in uncomplicated TBAD are established at the time of the initial event. The thickness of the dissection membrane universally increased in all patients over time, with decreasing motion artifacts.

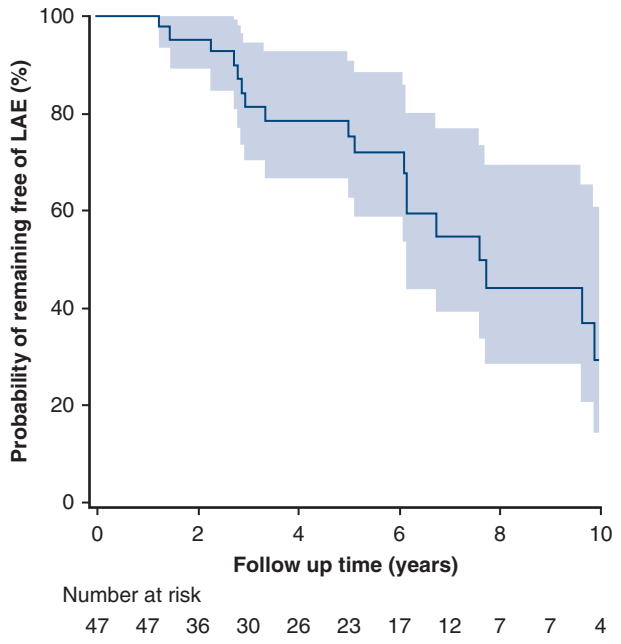


FIGURE 3. Kaplan-Meier curve showing the probability of remaining free from late adverse events over the entire follow-up period. The *blue* area denotes the 95% confidence band around the Kaplan Meier estimates. *LAE*, Late adverse event.

Univariable and Multivariable Analysis of Changes in Morphological Features Over Time

Median and IQR for each of the evolving morphological features at baseline and the regression coefficients of time and, if applicable, time-squared, are given in Table 2. The baseline values show the median values at time of inclusion accompanied by the IQR, and the coefficients show the average linear increase (or decrease in case of a negative coefficient) in the morphological feature per year after inclusion. In the event that a quadratic term was statistically significant, that coefficient was also presented well and would indicate a quadratic increase or decrease over time. The following morphological features showed significant changes over time: maximum major and maximum minor aortic diameter, size of the primary intimal tear (axial and sagittal), circumferential extent of FL, area of TL, area of FLT, and total aortic cross-sectional area. Coefficients of time could not be modeled for the following features due to the distribution and were not analyzed further: number of secondary tears and FLT grading.

The results of our univariable and multivariable analyses of the longitudinal predictors on LAEs are provided in

TABLE 2. Morphological features at baseline, and changes over time

Parameter	Baseline value, median (IQR)	Coefficient of time (per year), median (IQR)*	*P* value
Maximum major axis aortic diameter, mm	35.0 (33.0-38.5)	3.19 (2.21-4.17)	<.001
Maximum minor axis aortic diameter, mm	32.0 (30.0-36.0)	2.57 (1.67-3.47)	<.001
Size of intima tear axial, mm	7.0 (4.0-11.5)	1.34 (0.89-1.87)	<.001
Size of intima tear sagittal, mm	5.0 (2.0-8.0)	1.61 (1.11-2.11) −0.08 (−0.13 to −0.04)†	<.001 <.001
Number of secondary tears, n‡	1.0 (0.0-1.0)		
Circumferential extent of TL, °	103.0 (91.0-125.5)	−2.19 (−3.60 to −0.78)	.003
Circumferential extent of FL, °	257.0 (234.5-269.0)	2.19 (0.78-3.60)	.003
TL area, cm^2	2.5 (2.0-3.3)	0.32 (0.20-0.45) −0.02 (−0.03 to −0.01)†	<.001 <.001
FL area, cm^2	5.0 (3.7-6.4)	0.30 (−0.12 to 0.73)	.159
FLT area, cm^2	2.1 (0.0-3.6)	0.89 (0.41-1.38)	<.001
Total area, cm^2	8.0 (6.6-10.1)	1.61 (0.98-2.25)	<.001
FLT grading‡	1.0 (0.0-1.0)		
Number of ICAs from TL, n	7.0 (3.5-9.0)	−0.08 (−0.21 to 0.05)	.222
Number of ICAs from FL, n	8.0 (5.0-11.5)	−0.19 (−0.36 to −0.02)	.033
Total number of ICAs, n	16.0 (13.0-18.0)	−0.57 (−0.81 to −0.32) 0.04 (0.02 to 0.07)†	<.001 .002

Coefficients of time refer to the average linear (or quadratic) increase or decrease in each morphological parameter per year. *IQR*, Interquartile range; *TL*, true lumen; *FL*, false lumen; *FLT*, false lumen thrombosis; *ICA*, intercostal artery. *Computed using all available follow-up measurements, using mixed-effects regression. Estimates are accompanied by 95% confidence intervals. †Results of time-squared to accommodate nonlinear change over time. ‡Coefficient of time could not be modeled due to the distribution.

Table 3. Among the morphological features investigated, multivariable analysis revealed strong associations of the following morphological features with LAEs: increase in major aortic diameter (HR, 1.24 [95% CI, 1.13-1.37] per mm increase; $P < .001$), increase in minor aortic diameter (HR, 1.16 [95% CI, 1.07-1.25] per mm increase; $P < .001$), increase in the circumferential extent of the false lumen (HR, 1.05 [95% CI, 1.01-1.10] per degree increase; $P < .001$), increase in partial false lumen thrombosis area (HR, 1.39 [95% CI, 1.18-1.66] per cm^2 increase; $P < .001$), and increase in total area (HR, 1.18 [95% CI, 1.23-1.35] per cm^2 increase; $P < .001$). Tables E1-E7 present the coefficients of the baseline values of morphological features in addition to the multivariable adjusted longitudinal predictors.

DISCUSSION

The evolution of morphological features associated with LAEs in patients with initially uncomplicated acute TBAD is largely unknown. This is a crucial gap in our understanding of the subacute and chronic phases of the disease, because survivors of the initial event require life-long clinical follow-up and imaging surveillance, and it is plausible that ongoing changes to these morphological features would influence an individual patient's long-term risk profile. Our primary conclusions from serial imaging data in patients with uncomplicated TBAD are that some, but not all, baseline morphological predictors of LAE change over time; new prognostic features, such as partial false lumen thrombosis, may arise after the initiating event; and quantitative changes in morphological predictors over time convey potentially important prognostic information. Although many details remain to be elucidated, the fundamental implication of these observations is that imaging-based risk prediction models aimed at improving patient selection in the acute phase of an uncomplicated TBAD cannot necessarily be applied to the much larger number of expected follow-up imaging studies in the subacute and chronic phases of the disease. Examples of 5 of the 8 morphological features, and how they change over time are provided in Figure 4.

Our findings also suggest that morphological risk factors observed at any given time after the initial event need to be interpreted in the context of the entire preceding morphological evolution. For example, a 4-cm maximum aortic diameter may convey a different risk at baseline versus at a 2-year follow-up, and a 4-cm diameter at 1 year follow-up may also convey a different risk if the previous measurement at 12 months was 3 cm versus 3.5 cm. Interpretation of imaging findings that accounts for a patient's entire history of imaging findings is highly desired by clinicians, and our data support the need for analysis and interpretation of imaging data that include changes over time.[12,13]

Our study once again corroborates the importance of both maximum aortic diameter and a change in maximum aortic diameter over time as strongly predictive of LAEs. Others have demonstrated this as well.[8,14] It will be interesting to further investigate the interaction between size and growth in a larger cohort in the future.

The relative circumference—expressed in angular degrees—of the proportion of the outer aortic wall enclosing

TABLE 3. Associations between changes in morphological features over time and the occurrence of LAEs

Parameter	Univariable, HR (95% CI)	*P* value	Multivariable, HR (95% CI)*	*P* value
Maximum major aortic diameter, mm	1.21 (1.13-1.30)	<.001	1.25 (1.13-1.37)	<.001
Maximum minor aortic diameter, mm	1.16 (1.10-1.23)	<.001	1.16 (1.08-1.24)	<.001
Size of intima tear axial, mm	1.03 (0.99-1.03)	.145	NA	
Size of intima tear sagittal, mm	1.04 (0.98-1.10)	.171	NA	
Circumferential extent of TL, °	0.96 (0.94-0.98)	<.001	0.96 (0.94-0.98)	<.001
Circumferential extent of FL, °	1.03 (1.01-1.05)	.004	1.04 (1.01-1.06)	.004
TL area TL, cm^2	0.97 (0.68-1.38)	.874	NA	
FL area, cm^2	1.13 (1.02-1.25)	.017	1.06 (0.94-1.20)	.326
FLT area, cm^2	1.30 (1.16-1.46)	<.001	1.53 (1.25-1.88)	<.001
Total area, cm^2	1.18 (1.10-1.27)	<.001	1.26 (1.14-1.39)	<.001
Number of ICAs from TL	0.93 (0.80-1.08)	.330	NA	
Number of ICAs from FL	1.09 (0.95-1.25)	.235	NA	
Total number of ICAs	1.06 (0.92-1.23)	.407	NA	

HR, Hazard ratio; *CI*, confidence interval; *TL*, true lumen; *FL*, false lumen; *FLT*, false lumen thrombosis; *ICA*, intercostal artery; *NA*, not applicable (not significant in univariable analysis). *Association between the change in morphological feature over time and the time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis and corrected for the presence of connective tissue disease.

the false lumen has recently been shown to be an independent baseline predictor for LAEs.[5] It is not surprising that an increase of the false lumen circumference over time is also strongly associated with LAEs. Unfortunately, our analysis cannot determine whether the increase in false lumen circumference, or total aortic area, is also an independent risk factor over time, of whether it is simply associated with increasing diameter, which is driven almost exclusively by false lumen expansion. We acknowledge that the circumferential extent of the false lumen outer aortic wall measured in angular degrees is difficult to measure and interpret when the aortic cross-section becomes more elliptical rather than circular over time.

The primary intimal tear appears to grow larger over time, but this did not translate to an increased risk in our small cohort. We have not found the size of the primary intimal tear to be a significant baseline risk factor in uncomplicated TBAD,[5] although others have shown a higher rate of complications if both complicated and uncomplicated TBADs were included.[4] The hemodynamic effects of increasing primary intimal tear size while the dissection membrane becomes thicker and less mobile over time are currently unclear. Computational fluid dynamics modeling may improve our understanding of this evolution in the future.[15] Similarly, we observed an increase of secondary tears/communications between true and false lumen over time—again without a detectable effect on risk. It is possible that some of the subtle observations in our series reflect better detectability of preexisting small tears over time within an increasingly thicker and less mobile dissection membrane.

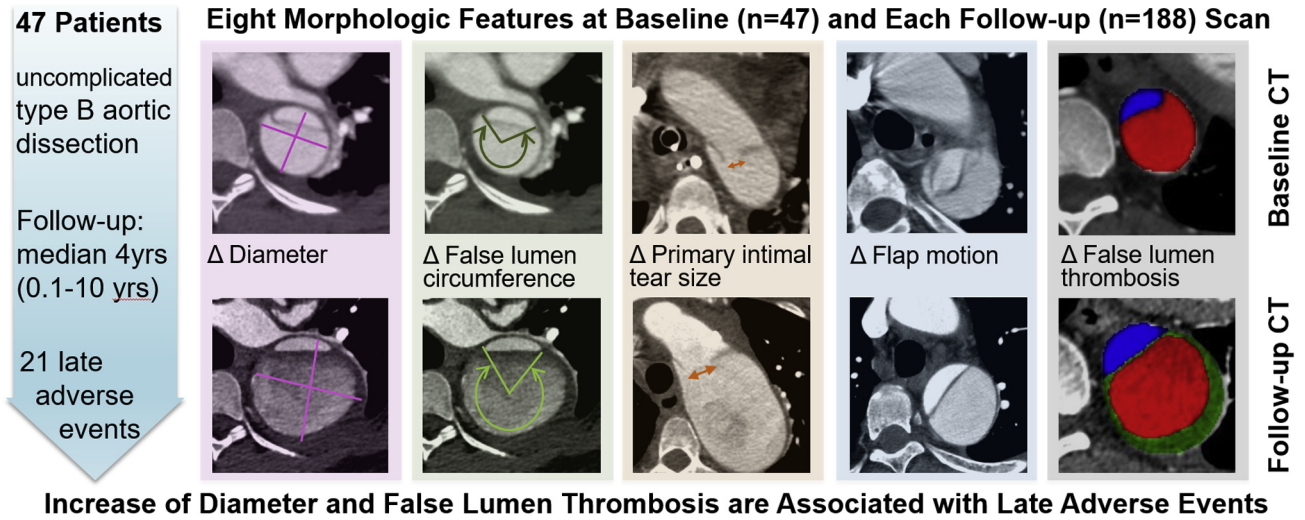


FIGURE 4. Five of the 8 morphological features, measured and recorded on baseline computed tomography (*CT*) scans (*top row*). Follow-up CT scans (*bottom row*) show how these features changed over time. In a cohort of 47 patients with initially uncomplicated type B aortic dissection, an increase in aortic diameter and the development of new or increasing partial false lumen thrombosis were associated with late adverse events.

Partial false lumen thrombosis has been described as a risk factor for adverse events in patients with type B dissection,[9] although this has not been a universal finding.[16] In our own experience, partial false lumen thrombosis was uncommon at baseline and did not predict LAEs.[5] In this analysis of serial imaging, however, we found that new development or increase of thrombus in the perfused false lumen is a significant risk factor. In contradistinction to the proposed hypothesis that partial thrombosis of the FL causes diminished outflow and thus increased FL mean pressure,[9] our findings are more closely compatible with the hypothesis that false lumen thrombus formation is the consequence of slow, stagnating blood flow[17] owing to poor FL drainage/outflow, which is associated with increased diastolic pressure and in turn faster aneurysmal degeneration.[8]

The main limitations of this study are the retrospective design and the relatively small population size. Although we analyzed a large number of CT datasets (n = 235), the lengthy processing time required to manually analyze each individual dataset prevented us from including a larger number of patients for serial analysis, and the study may be underpowered to identify additional morphological features associated with LAE. Further investigation of the quantitative assessment of aortic remodeling over time, which would be facilitated by new software-based tools for automatic or semiautomatic extraction of a wide range of anatomic features over time, will be needed. Machine learning algorithms also may take advantage of the currently unexploited information contained in modern high-resolution imaging datasets and uncover novel morphological prognostic factors.[18] Such developments are a prerequisite not only for expanding similar research efforts to larger cohorts, but also for using morphological features and their changes over time in a clinical setting. Finally, we were unable to correct the association of each of the longitudinal features on LAEs, for all other features measured over time owing to the fact that current joint models of longitudinal and time-to-event data have not been extended to allow inclusion of a large number of time-varying covariates. We did correct for baseline values of the important predictors, notably aortic diameter.

In conclusion, an increase in aortic diameter and increasing or new development of false lumen thrombus are both associated with LAEs in patients with initially uncomplicated TBAD. Future individual risk prediction models for patients with chronic dissection may be more accurate when based on both current and previous assessments, necessitating recalibration of model parameters with each follow-up encounter.

Conflict of Interest Statement

Dr Higashigaito is funded by an Early.Postdoc Mobility Grant (P2ZHP3_168559) from the Swiss National Research Foundation. Dr Willemink is supported by the American Heart Association (18POST34030192). This work was supported by National Institutes of Health Clinical and Translational Science Award UL1 RR025744. Dr Miller has financial relationships with Medtronic, Cardiovascular Division: Consultant and Edwards Lifesciences: Stanford PI for PARTNER and COMMENCE trials. All other authors have nothing to disclose with regard to commercial support.

References

1. Nienaber CA, Kische S, Rousseau H, Eggebrecht H, Rehders TC, Kundt G, et al. Endovascular repair of type B aortic dissection: long-term results of the randomized investigation of stent grafts in aortic dissection trial. *Circ Cardiovasc Interv*. 2013;6:407-16.
2. Buth J, Harris PL, Hobo R, van Eps R, Cuypers P, Duijm L, et al. Neurologic complications associated with endovascular repair of thoracic aortic pathology: incidence and risk factors. A study from the European collaborators on stent/graft techniques for aortic aneurysm repair (EUROSTAR) registry. *J Vasc Surg*. 2007; 46:1103-10; discussion: 1110-1.
3. Lee WA. Failure modes of thoracic endografts: prevention and management. *J Vasc Surg*. 2009;49:792-9.
4. Schwartz SI, Durham C, Clouse WD, Patel VI, Lancaster RT, Cambria RP, et al. Predictors of late aortic intervention in patients with medically treated type B aortic dissection. *J Vasc Surg*. 2018;67:78-84.
5. Sailer AM, van Kuijk SM, Nelemans PJ, Chin AS, Kino A, Huininga M, et al. Computed tomography imaging features in acute uncomplicated stanford type-B aortic dissection predict late adverse events. *Circ Cardiovasc Imaging*. 2017; 10:e005709.
6. Afifi RO, Sandhu HK, Leake SS, Boutrous ML, Kumar V III, Azizzadeh A, et al. Outcomes of patients with acute type B (DeBakey III) aortic dissection: a 13-year, single-center experience. *Circulation*. 2015;132:748-54.
7. Krol E, Panneton JM. Uncomplicated acute Type B aortic dissection: selection guidelines for TEVAR. *Ann Vasc Dis*. 2017;10:ra.17-00061.
8. Sailer AM, Nelemans PJ, Hastie TJ, Chin AS, Huininga M, Chiu P, et al. Prognostic significance of early aortic remodeling in acute uncomplicated type B aortic dissection and intramural hematoma. *J Thorac Cardiovasc Surg*. 2017; 154:1192-200.
9. Tsai TT, Evangelista A, Nienaber CA, Myrmel T, Meinhardt G, Cooper JV, et al. Partial thrombosis of the false lumen in patients with acute type B aortic dissection. *N Engl J Med*. 2007;357:349-59.
10. Spinelli D, Benedetto F, Donato R, Piffaretti G, Marrocco-Trischitta MM, Patel HJ, et al. Current evidence in predictors of aortic growth and events in acute type B aortic dissection. *J Vasc Surg*. 2018;68:1925-35.e8.
11. Rizopoulos D. *Joint Models for Longitudinal and Time-to-Event Data: With Applications in R*. Boca Raton, FL: CRC Press Taylor & Francis Group; 2012.
12. Elefteriades JA. Thoracic aortic aneurysm: reading the enemy's playbook. *Curr Probl Cardiol*. 2008;33:203-77.
13. Elefteriades JA, Rizzo JA, Coady MA. Thoracic aorta. *Radiology*. 1999;211:889.
14. Hosn MA, Goffredo P, Zavala J, Sharp WJ, Katragunta N, Kresowik T, et al. Analysis of aortic growth rates in uncomplicated type B dissection. *Ann Vasc Surg*. 2018;48:133-40.
15. Alimohammadi M, Sherwood JM, Karimpour M, Agu O, Balabani S, Diaz-Zuccarini V. Aortic dissection simulation models for clinical support: fluid-structure interaction vs. rigid wall models. *Biomed Eng Online*. 2015; 14:34.
16. Trimarchi S, Tolenaar JL, Jonker FH, Murray B, Tsai TT, Eagle KA, et al. Importance of false lumen thrombosis in type B aortic dissection prognosis. *J Thorac Cardiovasc Surg*. 2013;145(3 Suppl):S208-12.
17. Naim WNWA, Ganesan PB, Sun Z, Liew YM, Qian Y, Lee CJ, et al. Prediction of thrombus formation using vortical structures presentation in Stanford type B aortic dissection: a preliminary study using CFD approach. *Appl Math Model*. 2016;40:3115-27.
18. McBee MP, Awan OA, Colucci AT, Ghobadi CW, Kadom N, Kansagra AP, et al. Deep learning in radiology. *Acad Radiol*. 2018;25:1472-80.

TABLE E1. Association between change in maximum major aortic diameter adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
Maximum major aortic diameter, mm	1.24 (1.13-1.37)	<.001
Baseline values		
Maximum minor aortic diameter, mm	0.71 (0.55-0.92)	.010
Circumferential extent of TL, °	0.96 (0.94-0.99)	.003
FL area, cm^2	0.65 (0.41-1.02)	.060
FLT area, cm^2	0.72 (0.32-1.59)	.412
Total area, cm^2	1.55 (0.86-2.79)	.148

HR, Hazard ratio; *CI*, confidence interval; *TL*, true lumen; *FL*, false lumen; *FLT*, false lumen thrombosis. *Association between the change in a morphological feature over time and time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of FL was omitted for reasons of collinearity.

TABLE E2. Association between change in maximum minor aortic diameter adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
Maximum minor aortic diameter (mm)	1.16 (1.07-1.25)	<.001
Baseline values		
Maximum major aortic diameter, mm	0.77 (0.63-0.94)	.011
Circumferential extent of TL, °	0.97 (0.95-0.89)	.003
FL area, cm^2	0.67 (0.45-0.99)	.045
FLT area, cm^2	0.58 (0.24-1.38)	.219
Total area, cm^2	1.53 (0.94-2.48)	.086

HR, Hazard ratio; *CI*, confidence interval; *TL*, true lumen; *FL*, false lumen; *FLT*, false lumen thrombosis. *Association between morphological feature change over time and time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of FL was omitted for reasons of collinearity.

TABLE E3. Association between change in circumferential extent of TL adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
Circumferential extent of TL, °	0.96 (0.94-0.98)	<.001
Baseline values		
Maximum major aortic diameter, mm	1.00 (0.76-1.33)	.975
Maximum minor aortic diameter, mm	1.00 (0.73-1.36)	.998
FL area, cm^2	0.74 (0.52-1.07)	.112
FLT area, cm^2	0.56 (0.25-1.26)	.161
Total area, cm^2	1.35 (0.92-1.99)	.126

HR, Hazard ratio; *CI*, confidence interval; *TL*, true lumen; *FL*, false lumen; *FLT*, false lumen thrombosis. *Association between morphological feature change over time and time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of FL was omitted for reasons of collinearity.

TABLE E4. Association between change in circumferential extent of FL adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
Circumferential extent of FL, °	1.05 (1.01-1.10)	.012
Baseline values		
Maximum major aortic diameter, mm	0.92 (0.68-1.23)	.553
Maximum minor aortic diameter, mm	1.01 (0.74-1.38)	.954
FL area, cm^2	0.72 (0.50-1.04)	.079
FLT area, cm^2	0.53 (0.22-1.27)	.153
Total area, cm^2	1.36 (0.89-2.08)	.154

HR, Hazard ratio; *CI*, confidence interval; *FL*, false lumen; *FLT*, false lumen thrombosis. *Association between morphological feature change over time and time-to-occurrence of a LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of TL was omitted for reasons of collinearity.

TABLE E5. Association between change in area FL adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
FL area, cm^2	1.07 (0.95-1.21)	.266
Baseline values		
Maximum major aortic diameter, mm	0.87 (0.65-1.16)	.342
Maximum minor aortic diameter, mm	1.03 (0.74-1.42)	.875
Circumferential extent of TL, °	0.98 (0.95-1.00)	.040
FLT area, cm^2	0.76 (0.32-1.78)	.522
Total area, cm^2	1.08 (0.79-1.49)	.617

HR, Hazard ratio; *CI*, confidence interval; *FL*, false lumen; *TL*, true lumen; *FLT*, false lumen thrombosis. *Association between morphological feature change over time and time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of FL was omitted for reasons of collinearity.

TABLE E6. Association between change in area FLT adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
FLT area, cm^2	1.53 (1.25-1.88)	<.001
Baseline values		
Maximum major aortic diameter, mm	0.67 (0.48-0.93)	.017
Maximum minor aortic diameter, mm	1.49 (1.03-2.17)	.036
Circumferential extent of TL, °	0.98 (0.96-1.00)	.069
Area FL area, cm^2	0.87 (0.62-1.23)	.438
Total area, cm^2	0.74 (0.48-1.13)	.164

HR, Hazard ratio; *CI*, confidence interval; *FLT*, false lumen thrombosis; *TL*, true lumen; *FL*, false lumen. *Association between morphological feature change over time and time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of FL was omitted for reasons of collinearity.

TABLE E7. Association between change in total area adjusted for baseline values of other features and the occurrence of LAEs

Parameter	Multivariable HR (95% CI)*	*P* value
Total area, cm^2	1.26 (1.14-1.39)	<.001
Baseline values		
Maximum major aortic diameter, mm	0.74 (0.54-1.02)	.063
Maximum minor aortic diameter, mm	1.28 (0.93-1.77)	.130
Circumferential extent of TL, °	0.97 (0.95-0.99)	.008
FL area, cm^2	0.65 (0.47-0.88)	.006
FLT area, cm^2	0.60 (0.26-1.39)	.235

HR, Hazard ratio; *CI*, confidence interval; *TL*, true lumen; *FL*, false lumen; *FLT*, false lumen thrombosis. *Association between morphological feature change over time and time to occurrence of an LAE corrected for the baseline values of all other features significant in the univariable analysis. The circumferential extent of FL was omitted for reasons of collinearity.