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Inflammatory Cell Infiltrates in Acute and Chronic Thoracic Aortic Dissection

Darrell Wu, MD1,2,3,†, Justin C. Choi, MD1,2,†, Aryan Sameri, BS1,2, Charles G. Minard, PhD4, Joseph S. Coselli, MD1,2, Ying H. Shen, MD, PhD1,2, Scott A. LeMaire, MD1,2,3*

1Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, Texas; 2Department of Cardiovascular Surgery, The Texas Heart Institute, Houston, Texas; 3Department of Molecular Physiology and Biophysics, Baylor College of Medicine, Houston, Texas; and 4Dan L. Duncan Institute for Clinical and Translational Research, Baylor College of Medicine, Houston, Texas

Abstract

Background: Thoracic aortic dissection (TAD) is a highly lethal cardiovascular disease. Injury to the intima and media allows pulsatile blood to enter the media, leading to dissection formation. Inflammatory cells then infiltrate the site of aortic injury to clear dead cells and damaged tissue. This excessive inflammation may play a role in aneurysm formation after dissection. Methods: Using immunohistochemistry, we compared aortic tissues from patients with acute TAD (n = 11), patients with chronic TAD (n = 35), and donor controls (n = 20) for the presence of CD68+ macrophages, neutrophils, mast cells, and CD3+ T lymphocytes. Results: Tissue samples from patients with acute or chronic TAD generally had significantly more inflammatory cells in both the medial and adventitial layers than did the control samples. In tissues from patients with acute TAD, the adventitia had more of the inflammatory cells studied than did the media. The pattern of increase in inflammatory cells was similar in chronic and acute TAD tissues, except for macrophages, which were seen more frequently in the adventitial layer of acute TAD tissue than in the adventitia of chronic TAD tissue. Conclusions: The inflammatory cell content of both acute and chronic TAD tissue was significantly different from that of control tissue. However, the inflammatory cell profile of aneurysmal chronic TAD was similar to that of acute TAD. This may reflect a sustained injury response that contributes to medial degeneration and aneurysm formation.

Key Words

Inflammation · Thoracic aortic dissection · Macrophage · Mast cell · Neutrophil · T lymphocyte

Introduction

Aneurysm formation after thoracic aortic dissection (TAD) is a deadly cardiovascular disease and a major cause of morbidity and mortality [1]. Aortic dissections occur when pulsatile blood enters an intimal tear and causes the medial layer to split along the length of the aorta. Weakening of the aortic wall can be caused by medial degeneration, which is characterized by vascular smooth muscle cell depletion and elastic fiber depletion and fragmentation [2,3]. Concurrently, inflammatory cells can infiltrate the injured aortic wall, clear the dead cells, remove damaged matrix proteins, and remodel the extracellular matrix [4]. However, uncontrolled inflammatory processes can lead to tissue destruction in the aorta [5,6], which in turn may lead to the formation of an aneurysm after aortic dissection. The role of inflammation after dissection as a cause of aneurysm formation has not been well characterized.

Previous studies have shown that CD68+ macro-
phages [7], neutrophils [8], mast cells, and CD3+ [5,6] and CD4+ T lymphocytes [9] are significantly increased in the aortic wall of patients with abdominal aortic aneurysms or ascending thoracic aortic aneurysms (TAAs) (both heritable and sporadic), as well as in patients with Type A dissections [5,6]. However, the inflammatory infiltrates present in acute TAD and descending TAA due to chronic TAD are not well documented. In this study, we examined aortic tissues from patients with acute ascending TAD or descending aneurysms after TAD for the presence of CD68+ macrophages, neutrophils, mast cells, and CD3+ T lymphocytes in both early and late phases of the dissection. We hypothesized that chronic TAD tissues would exhibit reduced inflammation and an altered inflammatory cell profile compared to acute TAD tissues.

Materials and Methods

Study Enrollment and Tissue Collection

The institutional review board at Baylor College of Medicine approved this study. Informed written consent was obtained from all subjects. We enrolled 46 patients who underwent repair of an acute or chronic TAD and who did not have aortitis, dissection variants such as intramural hematoma or penetrating aortic ulcer, or a dissection caused by trauma. Tissue samples obtained within 14 days of TAD onset were considered acute (n = 11), whereas those obtained more than 60 days after TAD onset were considered chronic (n = 35); we did not enroll patients in whom tissue samples would be obtained during the subacute phase (ie, between 14 and 60 days after TAD onset). During dissection repair, we excised tissue samples from the outer wall of the false lumen. Control aortic tissues (n = 20) were obtained from organ or tissue donors who had no aortic aneurysm, dissection, coarctation, or prior aortic repair and no evidence of sepsis.

Histology and Immunohistochemical Staining

Aortic tissues were paraffin-embedded and sectioned. Endogenous peroxidase activity in aortic sections was quenched by 3% hydrogen peroxide treatment. Citric acid antigen retrieval was performed. Tissue sections were blocked in 5% normal horse serum and incubated overnight with primary antibodies (Table 1). Samples were then incubated with the appropriate biotin-conjugated anti-mouse IgG secondary antibodies (Vector Laboratories, Inc., Burlingame, CA, USA). Normal mouse immunoglobulin G (Vector Laboratories) served as the negative control for immunostaining. Inflammatory cells were visualized by using peroxidase substrate 3,3'-diaminobenzidine (DAB; Vector Laboratories), and cell nuclei were counterstained with hematoxylin (Sigma Aldrich, St. Louis, MO, USA). Image Pro-Plus 4.5 (Leica Microsystems, Bannockburn, IL, USA) was used to quantify the positive-staining inflammatory cells within the medial and adventitial layers. Three microscopic fields (400×) were randomly selected from each layer for analysis. Positive-staining areas were then normalized to an observed tissue area within the same sample.

Statistical Analysis

All quantitative data are presented as the mean ± standard deviation. Data were analyzed with SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA). The difference between the mean ratios of positively stained area (µm²) to observed tissue area (µm²) among the groups was compared by using the Mann-Whitney or Kruskal-Wallis nonparametric test with Bonferroni correction. The representative non-normal distribution of the positive-staining area was depicted by using boxplots with a five-point summary scale.

Results and Discussion

In response to aortic injury, inflammatory cells infiltrate the aortic wall to aid in tissue repair [4]. In this study, we characterized the inflammatory infiltrate observed in aortic tissues from acute and chronic TAD patients by means of immunohistochemistry; all TAD tissues showed significantly more CD68+ macrophages, neutrophils, mast cells, and CD3+ T lymphocytes in both the medial and adventitial layers as compared to the same vessel layer in aortic tissues from controls (Figs. 1A and 1B, 2A and 2B, 3A and 3B, and 4A and 4B, respectively). Moreover, we found a greater abundance of all inflammatory cell types in the adventitia than in the media (Figs. 1C, 2C, 3C, and 4C, respectively); this finding suggests that inflammatory cells infiltrate the aortic wall from the vasa vasorum into the media [10]. This increased inflammatory infl-

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trate at the site of either acute or chronic dissection suggests that an uncontrolled or chronic inflammatory response may contribute to aortic destruction and maladaptive remodeling of the aortic wall. Our findings support previous reports of a similar increase in inflammatory infiltrates in thoracic and abdominal aortic aneurysms [5,6], suggesting a possible shared mechanism of aortic degeneration among thoracic and abdominal aortic aneurysms and acute and chronic TAD.

Patient Characteristics

The clinical characteristics and demographics of the TAD patients and control donors are shown in Table 2. Patients with acute TAD tended to be younger, and the percentage of smokers was similar across the three groups. No patient in the chronic TAD group had diabetes. As expected, the time to surgery was longer for the chronic TAD patients than for the acute TAD patients (5 ± 3 days versus 1730 ± 2088 days), and we had a higher number of ascending aorta samples (n = 10) collected from acute TAD patients and a higher number of descending aorta samples (n = 20) from chronic TAD patients. The aortic diameters were similar for acute and chronic TAD patients.

Macrophages in TAD Tissues

Macrophages are one of the most abundant inflammatory cells in the media and adventitia of abdominal aortic aneurysms (AAAs), TAA [5,6], and TAD tissues [5]. Because they secrete proteases such as collagenases, elastase, and matrix metalloproteinase-9 (MMP-9) that directly destroy the extracellular matrix [7] and cytokines and chemokines such as interleukin 6 (IL-6) and monocyte chemotactic protein-1 (MCP-1) that recruit cells, macrophages are instrumental in maintaining and amplifying the inflammatory cascade [11]. Using a marker for phagocytic cells, our immunohistochemical analysis showed that more areas in the media and adventitia in acute and chronic TAD tissues. The tips of the projecting bars represent the minimum and maximum values, and the box depicts the interquartile range, with the solid middle line representing the median. Circles and asterisks represent 1.5× and 3× the interquartile range, respectively.
ings support the role of macrophages in ongoing aortic tissue destruction after dissection formation.

When evaluating the potential effects of macrophages, it is important to consider the two different subpopulations of macrophages: the proinflammatory M1 macrophages and the anti-inflammatory M2 macrophages. Studies have shown that an extensive presence of the cytotoxic M1 subtype can further contribute to tissue injury and destruction because these macrophages can release reactive oxygen species and nitric oxide synthase [13]. In contrast, M2 macrophages have been shown to resolve inflammation by inhibiting T cell proliferation, phagocytizing apoptotic neutrophils, reducing the production of proinflammatory cytokines, and secreting and stabilizing matrix components [13]. Therefore, comparing the levels of proinflammatory M1 macrophages and anti-inflammatory M2 macrophages in TAD tissue could help determine whether or not a chronic inflammatory state is likely to lead to an altered tissue homeostasis dominated by destructive factors.

Neutrophils in TAD Tissues

Neutrophils are key regulators of sterile vascular inflammation [14] and are capable of secreting serine proteases, cathepsins, and reactive oxygen intermediates that can damage the extracellular matrix [8,14]. In a mouse study, neutrophil depletion prevented AAA development [8], suggesting that neutrophil recruitment is critical for the development of aortic aneurysms. Furthermore, doxycycline therapy has been shown to improve proteolytic balance by reducing the neutrophil content in patients undergoing elective repair of AAA [15]. In the present study, we observed an increase in neutrophil cells in the media and adventitia of both acute and chronic TAD tissues (Fig. 2B). Our findings support those of Cohen et al. [16], who also reported an increase in neutrophil levels in AAA. Thus, we believe that neutrophils may play a role in the inflammatory cascade after an acute dissection and that increased neutrophil levels in chronic TAD tissues could suggest ongoing vascular injury, reflecting an acute-on-chronic inflammatory response that contributes to aneurysm formation.

Mast Cells in TAD Tissues

Like macrophages and neutrophils, mast cells have been shown to play a significant role in the development of AAA. Mast cells are capable of secreting chymases, which can activate matrix metalloproteinases, and angiotensin II, both of which contribute to aneurysm formation [17,18]. Additionally, mast cells can secrete tryptases and proinflammatory signaling factors, such as interferon-gamma (IFN\(\gamma\)), IL-6, and tumor necrosis factor-\(\alpha\) (TNF\(\alpha\)), which can lead to an increase in monocye infiltration, chemokine production, and vascular cell injury [19]. Furthermore, treatment with tranilast, a mast cell degranulation inhibitor, attenu-

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<th>Table 2. Characteristics of TAD Patients and Control Tissue Donors</th>
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<td>Bicuspid valve disease</td>
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<td>Aortic diameter (cm)*</td>
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*Data are presented as mean ± standard deviation.
**p-values comparing groups by using Kruskal-Wallis tests (continuous variables) or Fisher’s exact test (discrete variables).
ates aneurysm formation [20]. In the present study, we found a significant increase in mast cells in the aortic media and adventitia of both acute and chronic TAD tissues (Fig. 3B). Given the critical role of mast cells in vascular destruction, we believe they may be important contributors to the continued dilation and destruction of the aortic wall.

**CD3+ T Lymphocytes in TAD**

CD3+ T lymphocytes are capable of secreting cytotoxic mediators such as Fas/FasL and perforin, which can cause cell death and have been reported to be the most prominent inflammatory cell in the media of TAD [6]. Furthermore, CD3+ T lymphocyte activation can lead to the secretion of proteases that can weaken the aortic wall. For example, contact between mast cells...
and T lymphocytes can result in the release of MMP-9 from mast cells [21]. In the current study, we found that CD3+ T lymphocytes were significantly increased in the media and adventitia of acute and chronic TAD tissues compared to control tissues (Fig. 4B). Our findings, combined with those showing increased CD3+ T lymphocyte levels in both sporadic and heritable ascending TAA and Type A dissections [6], suggest that the pathogenesis of sporadic and heritable aneurysms and dissection may share a common immune mechanism.

**Media versus Adventitia**

In the traditional view of vascular inflammation, chemoattraction results in the movement of immune cells through the endothelium to the media. However, growing evidence indicates that the adventitia may play a more prominent role in maintaining an inflammatory response [22]. The adventitia is a major site of inflammatory cell accumulation, and an extensive infiltration of macrophages has been linked to aortic aneurysm development [23]. In this study, we found significantly more CD68+ macrophages, neutrophils, and CD3+ T lymphocytes in the adventitia than in the media in both acute and chronic cases of TAD (Figs. 1C, 2C, and 4C). The abundance of inflammatory cells in the adventitia indicates that the adventitia is a dynamic microenvironment intimately involved in aortic wall homeostasis.

**Eosinophils**

One cell type that was not studied was eosinophils. Eosinophils are capable of degranulating cytotoxic proteins that can damage tissue, produce superoxide and transforming growth factor-β, and be stimulated by neutrophils to produce proinflammatory cytokines to further perpetuate an inflammatory response [24]. Despite these numerous functions, the precise role of eosinophils in causing aortic aneurysms or dissection is not well understood, although eosinophils are present in the media of acute ascending dissection, suggesting a potential role of eosinophils in causing aortic dissection [25].

**Study Limitations**

Tissue samples in the TAD group were obtained from patients who had other underlying diseases in addition to the dissection, and some patients experienced dissection after aneurysm formation. Thus, patient heterogeneity and comorbidity factors may have affected the inflammatory response to dissection; however, this study was not powered to assess the clinical correlations between the degree of inflammatory infiltration and patient comorbidities. Furthermore, we evaluated only end-stage aortic tissue; the role of inflammatory cells in the early stages of the disease process needs to be studied to determine whether their presence is a contributing factor to
the initial development of TAD or solely a response to aortic injury after TAD. We also did not include an analysis of tissue from the interim subacute period after acute (<14 days) and before chronic (>60 days) dissection. Although these definitions of acute and chronic are arbitrary, tissue is more friable and difficult to operate on during this time frame, suggesting that there may be an immense amount of remodeling. For this reason, one might expect there to be even larger amounts of inflammatory cells present in these subacute cases than in acute or chronic cases. Additionally, we did not delineate subpopulations of inflammatory cells. Finally, technical limitations of our analysis based on the mean ratios of positively stained area (μm²) to observed tissue area (μm²) precluded a comparison of the relative distribution between cell types. Despite these limitations, the results of our study support the important role of the inflammatory response in TAD.

Conclusion

We observed a significant increase in CD68+ macrophages, neutrophils, mast cells, and CD3+ T lymphocytes in the media and adventitia of acute and chronic TAD tissues. The pattern of increase in inflammatory cells was similar in acute and chronic dissection tissue. The significant difference between the number of inflammatory cells seen in the medial and adventitial layers suggests that the cells infiltrate the media through the vasa vasorum. Overall, this study suggests that inflammation may play a role in tissue destruction and the development of aortic aneurysm after dissection.

Acknowledgments

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EDITOR’S COMMENTS AND QUESTIONS

Editor’s Comments:
The authors are to be congratulated on this important study, making stronger the link between inflammation, aortic aneurysm, and aortic dissection.

Editor’s Questions:
1. Why did you sample only the outer layer in your dissection patients? We know the dissection occurs in mid-media. Why not sample and examine the inner layer as well?

We are primarily interested in what drives aortic dilatation after aortic dissection has occurred. We focused on the outer wall of the false lumen because this is the region primarily responsible for aneurysm expansion and rupture in patients with dissection, and the region that would be the target for pharmacologic treatment designed to prevent dilatation after dissection. Changes involving the inner dissecting membrane (or dissection “flap”) would have limited clinical relevance in chronic dissection.

2. Is it fair to include a preponderance of descending dissections as your control group when the acute dissections were all ascending? Information is mounting that ascending and descending dissections are different diseases (embryology, genetics, morphology, pathophysiology [1,2], so one worries to have a disparate control group.

The editor makes a valid point. Our goal was to see whether the inflammatory response persists in chronic dissection patients. A set of patients with acute descending thoracic aortic dissection would be the ideal and proper controls for the group of patients with chronic descending thoracic aortic dissection; however, because it is very rare that these patients require open operative intervention, acutely dissected descending thoracic aortic tissue was not available for analysis. Although we acknowledge that acutely dissected aorta is not the ideal control, we believe it is a reasonable alternative at this stage, given that the inflammatory response to the tissue injury caused by acute dissection may be similar in different segments of the aorta, despite differences in underlying embryology, morphology, and pathophysiology; this supposition will require investigation.

3. You indicate that your controls were organ donors. Why did they have so much diabetes and stroke?

This was not intentional. Our main inclusion criterion for controls was that they had no evidence of aortic disease. Many of the control subjects were donors of non-vital organs and tissues. Selecting a control group with an age that matched the age of...
our patient population (>65 yr) resulted in a relatively high prevalence of comorbidities.
4. Is it fair to say that your hypothesis that chronic dissection patients would have less inflammation than acute dissection patients was not borne out? Any comments on this?
   Our findings did not support our original hypothesis. In inflammation, a basic tenet is that after 24-48 hours, the predominant inflammatory cell infiltrate is macrophages, which progressively phases out over the next 7-14 days. We were surprised that the entire spectrum of inflammatory cells was present even in chronic dissection tissue samples, suggesting a sustained active inflammatory response.
5. Does the association you show us between inflammation and dissection inform us about causation? That is to say, which is the chicken and which is the egg? Does the inflammation come first, or the dissection?
   We do not believe our findings provide information about the role of inflammation in the initiation of aortic dissection. Although aortic wall inflammation may certainly be a factor in the initial intimal/medial tear from which the dissection propagates, we purposely focused on tissue from the outer wall of the false lumen distal to the initial entry site to better understand the inflammatory response to dissection. We view the acute longitudinal splitting of the media as a form of severe vascular wall trauma that would be expected to spark a major acute inflammatory response, and we were particularly interested in how the inflammatory cell profile might change when moving into the chronic phase. Our findings suggest that a continued inflammatory response may contribute to progressive weakening of the outer aortic wall in patients who develop aneurysms caused by chronic dissection.

References

Abstract
Background: Abdominal aortic aneurysm (AAA) growth is a complex process that is incompletely understood. Significant heterogeneity in growth trajectories between patients has led to difficulties in accurately modeling aneurysm growth across cohorts of patients. We set out to compare four models of aneurysm growth commonly used in the literature and confirm which best fits the patient data of our AAA cohort. Methods: Patients with AAA were included in the study if they had two or more abdominal ultrasound scans greater than 3 months apart. Patients were censored from analysis once their AAA exceeded 5.5 cm. Four models were applied using the R environment for statistical computing. Growth estimates and goodness of fit (using the Akaike Information Criterion, AIC) were compared, with \( p \)-values based on likelihood ratio testing. Results: Of 510 enrolled patients, 264 met the inclusion criteria, yielding a total of 1861 imaging studies during 932 cumulative years of surveillance. Overall, growth rates were: (1) 0.35 (0.31, 0.39) cm/yr in the growth/time calculation, (2) 0.056 (0.042, 0.068) cm/yr in the linear regression model, (3) 0.19 (0.17, 0.21) cm/yr in the linear multilevel model, and (4) 0.21 (0.18, 0.24) cm/yr in the quadratic multilevel model at time 0, slowing to 0.15 (0.12, 0.17) cm/yr at 10 years. AIC was lowest in the quadratic multilevel model (1508) compared to other models (\( P < 0.0001 \)). Conclusion: AAA growth was heterogeneous between patients; the nested nature of the data is most appropriately modeled by multilevel modeling techniques.

Key Words
Abdominal aortic aneurysm · Growth rate · Quadratic · Multilevel modeling

Introduction
An abdominal aortic aneurysm (AAA) is a focal dilation of the abdominal aorta, greater than 3 cm in diameter or 1.5 times the diameter of the adjacent normal aorta. In clinical practice and in the UK AAA National Screening Programme (http://aaa.screening.nhs.uk), once the infrarenal aorta reaches 3.0 cm in its maximal anteroposterior (AP) diameter, it is classified as aneurysmal. The event(s) that trigger AAA development remain unknown. Important clinical risk factors include male sex, smoking, hypertension, and a family history of the condition [1]. Once established, AAA progressively evolves toward rupture, which confers high mortality.

Rupture risk is positively associated with aneurysm...
size. Presently, the mainstay of clinical management involves active monitoring, smoking cessation therapies, and cardioprotective medication, with prophylactic repair once the annual risk of rupture outweighs the mortality risk of intervention. This intervention threshold is currently set at 5.5 cm (on abdominal ultrasonography) in otherwise fit patients, based on randomized trial data [2]. Aneurysm screening is effective at reducing mortality from AAA rupture in men and is being increasingly adopted in many developed countries [3]. The recent report from the RESCAN collaborators suggests surveillance intervals could be safely increased, with significant cost savings [4].

Aneurysm growth is a complex process that is not necessarily linear and remains a relatively poorly explored area in the literature. Many authors have noted significant heterogeneity in aneurysm growth patterns between patients [5–7]. This has led to difficulties in attempts to report pooled growth estimates for patient cohorts [7]. A variety of growth modeling strategies have been reported previously [8], but direct comparisons within a single-center patient cohort are lacking. The aims of this study were (1) to compare a range of models to estimate aneurysm growth and (2) to confirm the most appropriate modeling strategy for estimating growth in a cohort of patients by testing the goodness-of-fit of each model to data derived from our patient cohort.

**Materials and Methods**

**Patients**

Consecutive patients referred to our institution, a university hospital vascular surgery unit, serving a local population of 800,000 in the United Kingdom with a diagnosis of AAA between January 1, 2003 and April 31, 2010 were invited to participate in the Leeds Aneurysm Development Study (LEADS) on a voluntary basis. The inclusion and exclusion criteria for LEADS have previously been reported [9–11]. Ethical approval was given by the institutional ethics committee (Project Reference: 03/142). At recruitment, all patients gave written, informed consent and completed a standardized health questionnaire which was administered face-to-face by a research nurse (A.J.).

**Imaging**

Maximal aortic diameter in the anteroposterior plane was measured with B mode abdominal ultrasound (USS) using an Acuson Antares scanner (Siemens Healthcare, Malvern PA, USA). Calipers were placed on the outer wall of the sac, producing outer wall- to-outer wall (OTO) maximal aneurysm diameter measurements, which reflected departmental practice during the study period. Scanning intervals were based on the UK Small Aneurysm Trial [12], arranged by the clinician in charge of the patient’s care. Enrollment in the study had no impact on normal clinical care. Patients received surveillance until they underwent aortic repair, died, or withdrew from the study. Scans performed in our department prior to recruitment were also included, with patient consent, and thus the earliest imaging study dates from February 1994. All USS were performed by experienced vascular sonographers; variability for the department has been previously reported [13].

**Inclusion and Exclusion Criteria**

Patients from LEADS were included in the present study if they had an infrarenal abdominal aortic aneurysm (defined as an infrarenal aortic diameter ≥ 3 cm or 1.5 times the diameter of the adjacent aorta) and agreed to participate in the study [10,11]. We only included imaging data from patients with two or more USS performed a minimum of 3 months apart, while the aneurysm was ≤ 5.5 cm in maximal diameter for the modeling comparisons. Patient data were censored from the analysis once the aneurysm exceeded the 5.5 cm intervention threshold on USS, as it is possible that growth patterns in large aneurysms, above the intervention threshold, differ from those beneath it, and this falls outside the remit of the present study.

**Statistics**

We applied four growth models to the data: (1) simple growth/time analysis, (2) ordinary linear regression model, (3) linear multilevel model (MLM), and (4) quadratic MLM. All models were constructed by a biostatistician (P.B., T.J.) using the R environment for statistical computing (www.R-project.org).

Simple growth/time analysis (1) involved dividing the difference between the first and last aortic diameters (centimeters) by the length of time between the two measurements (years). An ordinary linear regression model (2) [14] was fitted with aortic diameter as the response element and time from the initial scan as the predictor. A parametric, linear MLM (3) with two levels and measurements nested within patients [15,16] was fitted by full maximum likelihood, with aortic diameter as the response element and time from the initial scan as the fixed predictor. A random, normally distributed intercept term and a random, normally distributed slope term were added for each patient. A quadratic MLM (4) [15,16] was also fitted using the same basic structure as the linear MLM, with the addition of both a fixed effect and a random, normally distributed slope term that were quadratic in time (modeled up to 10 years).

Model comparisons were conducted using the Akaike Information Criterion (AIC) together with p-values based on likelihood ratio testing. Lower values of AIC represent a more parsimonious fit of the model to the data set and provide a measure of how well the model represents the patient data on which it is based. Data are presented as mean (95% confidence intervals) or mean ± standard deviation unless otherwise stated. A p-value < 0.05 was set as the predetermined level of statistical significance.
Study Population
Five hundred and ten patients with AAA were enrolled in LEADS during the study period. Of these, 264 met the inclusion criteria for the present analysis. Data were available from 1861 suitable imaging studies for modeling comparison. Each patient contributed an average of 7.6 USS measurements to the study during 932 cumulative years of surveillance (mean 3.5 ± 2.5 years/patient). The mean aneurysm size at recruitment to the study was 3.8 ± 0.7 cm, increasing to 4.7 ± 0.7 cm at the end of the study period. The mean age of the study population was 74 ± 2 years at recruitment; 81% were men. The results of the medical questionnaire are provided in Table 1. As expected, there was a high proportion of hypertensive ex-smokers (mean pack years smoked, 43) with a range of cardiovascular comorbidities. Of these, 197 of 264 (74.6%) were receiving antplatelet therapy, 175 of 264 (66.3%) statins, and 181 of 264 (68.6%) at least one antihypertensive medication (beta blockers, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, or calcium channel blockers).

Growth Modeling Estimates
As expected, aneurysm growth was heterogeneous across the study population. Illustrative scatter plots of patients exhibiting slow, moderate, and rapid aneurysm growth are provided in Figure 1. Overall growth estimates for the cohort by model were: (1) simple growth/time model: 0.35 (0.31,0.39) cm/yr, (2) ordinary linear regression model: 0.056 (0.042,0.068) cm/yr, (3) linear MLM: 0.19 (0.17,0.21) cm/yr, and (4) quadratic MLM: 0.21 (0.18,0.24) cm/yr, at time zero (see Fig. 2), slowing to 0.15 (0.12,0.17) by year 10 (see Fig. 3). The residuals were normally distributed for models (2), (3), and (4).

Goodness-of-Fit Analysis
It is not possible to calculate the AIC for the simple growth/time model (1). For the ordinary linear regression model (2), AIC: 3819. For the linear MLM (3), AIC: 1527, \(P < 0.0001\) compared to model (2). For the quadratic MLM (4), AIC: 1508, \(P < 0.0001\) compared to model (2) and \(P < 0.0001\) compared to model (3).

Discussion
In this study, we have modeled aneurysm growth in a cohort of 264 patients with infrarenal AAA below or at the intervention threshold and compared four statistical modeling approaches which have been previously used in the literature. We have demonstrated that the four different models applied to our data produced heterogeneous estimates of aneurysm growth.

The simple growth/time calculation produced an overestimate of growth compared to the MLM estimate. We relate this to the observation that the last scan in the series is more likely to be an overestimate (due to observer variability in measurement) that triggered intervention and hence was never corrected by further scans. When used as the second of two data points to calculate growth, this leads to bias in favor of overestimation. It is also possible that negative growth rates could be produced by this method; however, we did not observe this in our analysis. Further, the method is significantly weakened by the fact that it ignores the majority of the data points (71.6% of data points in our study are ignored by this method, for example). AIC cannot be calculated for this method of growth estimation as there is no statistical model underlying the growth process that can be tested.

When applied to our data, an ordinary linear regression model underestimated growth as compared to all other models with heavily autocorrelated residuals. We hypothesize that this may be related to the differences in individual growth trajectories that are attenuated when trajectories are pooled across patients, coupled with the fact that the model ignores the
multilevel structure of these data. Patients with slow-growth AAA tend to have a larger number of scans in total, which may compound bias in the model toward slow growth. Using a linear regression model does include all data, in contrast to the growth/time calculation, but analyzes all scan data for all patients together. This represents a statistical error; the assumptions of the model are not met by these data, as scans from the same patient are related through growth and thus are not independent, as is required for simple linear regression analysis. We suggest that this is therefore an invalid method of modeling this type of data, the growth estimate of which is completely inaccurate and should be ignored.

In MLM, each patient contributes to the overall growth estimate, but an individual regression line is modeled for each patient. The effects of covariates can then be added as interactions with the overall growth estimate observed (although this covariate analysis requires a large number of patients). MLM better represents the correlated nature of these data, and an improved AIC is apparent for the linear MLM as com-
pared to a linear regression model. However, a linear MLM still presumes aneurysm growth to be a linear process, and this is not necessarily the case [17]. We therefore also tested a quadratic basis to the MLM. In our patient cohort, a quadratic basis to MLM demonstrated a small but significant improvement in AIC when compared to a linear MLM. Both the linear and quadratic MLM demonstrated significantly improved AIC compared to the ordinary linear regression model. It is noteworthy that the growth estimate in the quadratic MLM slows over time. This is not suggesting that aneurysm growth slows in individual patients, but rather reflects the observation in the fixed effects part of the model, that patients with slower growing aneurysms will remain in the cohort for longer time periods, whereas those with rapidly growing aneurysms will leave the cohort to undergo repair.

Our data support the notion that AAA growth exhibits significant variation between patients, is not necessarily linear, and is more suitably represented by MLM techniques. Our AIC data suggest that quadratic as opposed to linear modeling strategies most accurately represent the growth of AAAs within a cohort of patients over time. However, it is difficult to be certain if the quadratic MLM provides a more accurate growth estimate than a linear MLM or simply better detects the selection effects introduced by slow-growing aneurysms persisting in the data set for a longer time. Our data add weight to the previous work using MLM techniques, and we suggest that future studies aiming to identify factors which may influence growth must use MLM to reach valid conclusions. Relatively few groups have previously used MLM [5,18–21], possibly because this requires access to a suitable experienced biostatistician, which is not always possible. Reassuringly, the MLM generated growth estimates for our patient cohort which were similar to previous high-quality reports using large patient numbers with linear MLM [17,19].

There are clear limitations to this work. We have used a cohort of patients from a single center in the UK. Our findings are therefore specific to this cohort of patients, which may differ compared to other AAA patient groups around the globe. While the overall sample size was relatively small, it was large enough to estimate the fixed effects of the model [22]. It would have been beneficial to include relevant clinical risk factors for AAA (e.g., gender, smoking, hypertension) in the model; however, the sample was likely underpowered for looking at interaction terms, as would be required for subgroup analysis, so this was not possible. It is noteworthy that a proportion of patients recruited to the study were excluded from the growth modeling analysis (48%). These patients tended to have an incidental large aneurysm detected with a single scan that went straight for intervention; thus no growth data were available. Another problem is the fact that patients with fast-growing aneurysms are selected out of the data (to go for intervention) and thus have fewer data points included. Joint modeling [23,24] is an appealing approach to try to broach this problem, as it would allow correction for this selection effect. Joint modeling allows the analysis of the data taking into account both the autocorrelation in the repeated measures as well as the time-to-event outcome (aortic intervention). We chose to censor any measurement data from AAAs above the traditional intervention threshold of 5.5 cm. Very little is known about the growth patterns of these large AAAs and it is possible that these aneurysms exhibit a growth pattern different from smaller aneurysms which would require an alternative modeling technique. This is an important, separate area for further study. We also set a minimum standard of scans required to meet inclusion criteria (two or more USS which were at least 3 months apart). This approach was taken to ensure enough data were available to estimate a growth trajectory for each patient. Few patients contributed only the minimum number of scans (n = 16, 6% of the study population), with the average contribution being 7 scans per patient. It has been established that USS aneurysm measurement from inner wall to inner wall (ITI) is more reproducible than OTO [25]. As our study began in 2003, we have used OTO measurements for the purposes of the present analysis. The data used for analysis reflect the duration of OTO measurement policy in our department. All patients now receive ITI measurements as per the UK National AAA Screening Programme (http://aaa.screening.nhs.uk), but none of these measurements were included in the present analysis.

Conclusion

AAA growth is a complex process that varies significantly patient-to-patient. Between 3.0 and 5.5 cm, the heavily nested structure of the data is best represented with multilevel modeling techniques. Further work should focus on joint modeling approaches and on aneurysms above the intervention threshold.
Acknowledgments

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References


Dear Editor:

The authors [1] have provided some interesting results and furthered understanding of the statistical challenges and appropriate procedures for estimating aneurysm growth rates. We have learned a great deal from this study and applaud their efforts. But after reviewing their study carefully, we feel that an exponential modeling approach, as applied in some previous research [2,3], is preferable because it models a more realistic pattern of aneurysm growth, in which growth depends not only on duration but on initial aneurysm size. The exponential model posits that the last measured aneurysm size, \( A_r \), and the first measured size, \( A_p \), are related as follows:

\[
A_r = A_p e^{\beta T},
\]

where \( T = \) the time between the first and last tests and \( \beta \) is a coefficient to be estimated. This approach is implemented by taking the natural logarithm of both sides of Equation 1 and then estimating by ordinary least squares (OLS), allowing for no intercept term. This functional relationship has the properties that aneurysm growth is larger, the greater the initial aneurysm size and the longer the patient is followed.

One criticism of this approach is that it does not use all available data, such as when patients have more than two imaging studies. But if patients have several measured sizes, one may still apply this method, taking advantage of these multiple measurements to enlarge the sample size. Suppose, for example, that there are three measured sizes for the same patient and that we also know the dates for each measurement. One can then obtain two observations for this patient. The first observation relates the difference between the 1st and 2nd size to the time between the first and second tests, while the second relates the difference between the 2nd and 3rd size to the time between the second and third tests. For the first observation, the first size can be regarded as \( A_f \) and the second size can be regarded as \( A_p \), where \( T \) is the time between the first and second tests according to Equation 1 above. For the second observation, the second size can be regarded as \( A_p \) and the third size can be regarded as \( A_f \), where \( T \) is the time between the second and third tests. However, this modeling approach may suffer from the fact that the same patient appears in the data set more than once (Gujarati and Porter 2009). The error terms in the linear regression will then be correlated because several error terms are from the same patient. A model clustering the error terms and controlling for autocorrelation should be applied. Clustering the error terms enables us to control for the correlations between several error terms from the same patients. Autocorrelation occurs because the different observations from the same patients are also correlated. For example, the size difference for the first observation is correlated with that of the second observation from the same patient. This approach using all available data increases statistical power and precision of the estimates. However, it may exacerbate selection effects. For example, if patients with multiple imaging studies tend to have stable, slow-growing aneurysms while fast-growing aneurysm patients are selected out for surgery after fewer imaging studies, this approach will overweight the slow-growing aneurysms, biasing growth estimates downward.

In prior correspondence, the authors have argued that the exponential model is no better than the OLS estimates they provided and which they considered to be inferior to their preferred models; namely, the linear multilevel model (MLM) and quadratic MLM models. The authors also noted that they estimated the exponential model, finding that for a person with a 1 cm aneurysm, the annual growth would be 0.052 cm, increasing to 0.088 cm after 10 years. However, this example is misleading because it uses patients with aneurysm sizes that were not in the database. To be enrolled in their study, patients had to

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have an initial aneurysm size $\geq 3$ cm or 1.5 times the size of the adjacent aorta. It seems doubtful that more than a few, if any, patients with an aorta $= 1$ cm were included in the analysis. It would be more reasonable and informative to apply aneurysm sizes actually observed in the data to the exponential model estimates.

When one does this, their results using the exponential model indicate the following:

<table>
<thead>
<tr>
<th>Initial Aneurysm Size</th>
<th>Annual Growth</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 cm</td>
<td>0.16 cm</td>
</tr>
<tr>
<td>4 cm</td>
<td>0.21 cm</td>
</tr>
<tr>
<td>5 cm</td>
<td>0.26 cm</td>
</tr>
<tr>
<td>5.5 cm</td>
<td>0.29 cm</td>
</tr>
</tbody>
</table>

These growth rates are consistent with the values in their preferred models; namely, the MLM linear and MLM quadratic models. But, unlike their models, the exponential approach shows that growth increases as the aneurysm size is greater, which we believe makes compelling clinical and anatomical sense. Their MLM linear model concludes that growth is the same regardless of aneurysm size, while the MLM quadratic model estimates that growth actually declines over time as the aneurysm is increasing in size. We find this implausible and believe it may just be tracking a selection effect in the data, e.g., patients with large unstable aneurysms are differentially selected out for surgery, leaving a disproportionate share of large aneurysm patients whose aneurysms are more stable.

The authors do not include further imaging studies once a patient has an imaging study that measures the aorta as being $\geq 5.5$ cm. They note that this is because growth of large aneurysms may be different. We concur and, in fact, their statement on this point is really an admission that aneurysm growth does depend on aneurysm size, most probably with larger aneurysms growing faster. But none of their models capture this effect. The exponential modeling approach does.

The authors’ decision to exclude further imaging studies once patients have passed the size threshold for intervention may, however, be justifiable on the grounds that it mitigates selection effects. If patients with large unstable aneurysms are differentially selected out for surgery, including the remaining large stable aneurysms in the study may exacerbate selection effects, and one might erroneously estimate that larger aneurysms grow more slowly. While statistical methods for dealing with selection effects are well known in the literature [4], this would require estimating an equation predicting the probability that a patient is selected out for surgery in addition to estimating growth. The data requirements to implement this selection correction, both in terms of sample size and variables needed, can be quite formidable.

### References


Cardiovascular Collapse During Transcatheter Aortic Valve Replacement: Diagnosis and Treatment of the “Perilous Pentad”

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Abstract
Transcatheter aortic valve replacement (TAVR) has, without a doubt, brought an unprecedented excitement to the field of interventional cardiology. The avoidance of a sternotomy by transfemoral or transapical aortic-valve implantation appears to come at the price of some serious complications, including an increased risk of embolic stroke and paravalvular leakage. The technical challenges of the procedure and the complex nature of the high-risk patient cohort make the learning curve for this procedure a steep one, with the potential for unexpected complications always looming. Although most commonly relating to vascular access, these complications can also result from prosthesis-related trauma or malposition, or from unanticipated trauma from the pacing wire or the super stiff wire. Sudden and unexplained hypotension is often the earliest indicator of major complication and must prompt an immediate and detailed exclusion of five major pathologies: retroperitoneal bleeding from access site rupture, aortic dissection or rupture, pericardial tamponade, coronary ostial obstruction, or acute severe aortic regurgitation. In most cases, these can be dealt with quickly, and by percutaneous means, although open surgery may occasionally be necessary. Increased operator and team experience should make prevention and recognition of these catastrophic complications more complete. For this reason, the importance of specific training, such as that provided by the valve manufacturers through workshops and proctorship, cannot be overemphasized. It is essential that all operators, and indeed all members of the implant team, exert extreme vigilance to the development of intraprocedural complications, which could have rapid and potentially lethal consequences. Greater experience with an improved understanding of these risks, along with the development of better devices, deliverable through smaller and less traumatic sheath technology, will undoubtedly improve the safety and, potentially, widen the applicability of TAVR in the future. Forthcoming innovations include a newer generation of the valves with operator-controlled steerability to facilitate negotiation of tortuous aortic anatomy, as well as fully retrievable and resheathable devices to accommodate the events of dislocation or embolization. The fact that Transcatheter aortic valve implantation (TAVI) is new implies learning from experience but also from mistakes. The TAVI team must be vigilant to recognize and diagnose intraprocedure severe hypotension. The “perilous pentad” of catastrophic causes must be constantly borne in mind: retroperitoneal bleeding from access site rupture, aortic dissection or rupture, pericardial tamponade, coronary ostial obstruction, and acute severe aortic insufficiency.

Key Words
Transcatheter aortic valve replacement · Complications · Aortic valve

Introduction
Transcatheter aortic valve replacement (TAVR) has become a major clinical reality in the management of
patients with severe aortic stenosis who are deemed to be a high or indeed a prohibitive surgical risk [1,2]. Current understanding of the likely complications associated with this procedure is rapidly evolving. TAVR adverse events differ markedly from those related to surgical intervention.

Awareness of how complications occur may help in their recognition, management, and ultimately, avoidance, thus improving patient outcomes and facilitating the safe application of this novel therapy.

TAVR continues to be associated with the potential for serious complications [3,4] including vascular injury, stroke, cardiac injury such as heart block, coronary obstruction, cardiac or aortic perforation, paravalvular leak, and valve misplacement.

Within this article we review the complications of TAVR and discuss possible prevention, diagnosis, and management.

**Hypotension**

Although, most often, relieving aortic stenosis is associated with spontaneous improvement of left ventricular (LV) function and hemodynamics, patients with severe aortic stenosis may be extremely sensitive hemodynamically. This is particularly true in the presence of coronary artery disease and LV systolic or diastolic dysfunction. Whatever the primary cause, hypotension or tachycardia may initiate a downward spiral of ischemia and severe pump failure. Vasopressor agents (phenylephrine or norepinephrine), which maintain adequate perfusion pressure, are often helpful. Chronotropic and inotropic agents should be avoided as they tend to increase myocardial oxygen demands, which may intensify myocardial ischemia and induce a downward spiral which may not be recoverable without cardiopulmonary bypass [5].

Unexplained severe hypotension should prompt consideration for an immediate diagnostic strategy to identify and treat the cause [6] (Table 1), which enumerates the “perilous pentad” of potential catastrophic sources of hypotension during TAVR. This checklist may serve as a useful mental map during the acute hypotensive event.

*Retroperitoneal Bleeding from Access Site Rupture*

The relatively large diameter of the delivery catheter, the frequent presence of severe arteriosclerosis, along with the common factor of patient fragility can combine to create major vascular problems at the access site. Access for the delivery sheath has proven to be a major limitation of transarterial TAVR. Early systems used 22 gauge to 25 gauge French sheaths (outer diameter 9-10 mm), and in the absence of adequate screening, the incidence of arterial dissection and perforation was relatively high [6,7].

To determine the feasibility of an arterial approach, careful and meticulous assessment of the arterial tree—using multi-slice computed tomography and angiography—is mandatory. The images should be used to evaluate the presence and severity of arterial access pathology and arterial size [8,9].

Minimal lumen diameter, as well as the amount and distribution of atheroma, tortuosity, and calcification, will determine the risk of vascular injury related to sheath insertion. Ideally, the minimal lumen diameter should exceed the diameter of the delivery system.

As a rule, in borderline cases, regarding size or significant pathological findings, one should use access alternatives, which include the apical, subclavian, open iliac, or ascending aorta approaches [9,10]. Another option in such circumstances is reconstruction of the ilio-femoral axis with stents or grafts. Although a large body of knowledge exists for the apical procedure, clinically documented experience with other approaches is still rapidly growing.

After uncomplicated vascular closure, ilio-femoral angiography should be performed from the contralateral femoral access site, which allows rapid identification and, if necessary, ongoing management of vascular complications.

Dissection or perforation of the ilio-femoral arteries may occur in the presence of excessively traumatic sheath insertion. Dissection of the ascending or descending aorta can similarly occur due to catheter trauma. Hypotension, hypovolemia, or cardiac tamponade are the common clinical scenarios whenever a vascular perforation or dissection takes place [11].

Retroperitoneal hemorrhage is one of the dramatic potential complications of TAVR. Successful management requires a high level of suspicion should sudden unexplained hypotension occur [12].

When the large arterial sheath is occlusive, perforation may become evident only after sheath removal. Volume expansion and angiographic assessment should be performed without delay.
Immediate reinsertion of the occlusive sheath over a guide wire or placement of a highly compliant occlusion balloon, proximal to the area of suspected perforation, typically provides rapid and relatively reliable control of bleeding, allowing time for definitive management [11]. Covered stents or percutaneous endografts might serve as adequate therapy and should be available in the catheterization laboratory for prompt intervention, although formal surgical repair might be necessary.

**Aortic Dissection or Rupture**

Unexplained hypotension after balloon dilation or valve expansion should prompt echocardiographic or angiographic assessment of the LV outflow tract and aortic root.

Rupture of the aortic annulus can occur following aortic balloon valvuloplasty or valve deployment. Accurate choice of the valve and balloon size, avoiding excessive balloon dilation and valve oversizing, may decrease the likelihood of this uncommon but deadly complication. Particular attention is required where the annulus and/or subannular tissues are markedly calcified or when the root is unusually small [14,15]. These same traumatic forces during forceful manipulation of the aortic root can produce aortic dissection, with distal propagation from the aortic root. Like aortic rupture, this should be sought and diagnosed from the intraoperative transesophageal echocardiogram. Open surgical correction will usually be required.

**Pericardial Tamponade**

The reported incidence of tamponade after TAVR varies from 0% to 7%. Typically, pericardiocentesis is adequate; however, thoracotomy might be required. The use of a stiff wire with an appropriately shaped curve and a standard J-curve at the tip is likely to be

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**Table 1. Causes of Severe Intraoperative Hypotension During TAVR (and Other Less Acute Complications)**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Retroperitoneal bleeding from iliac artery access site rupture</td>
<td>Balloon occlusion&lt;br&gt;Surgical control</td>
<td>Precise imaging of access iliofemoral vessels can decrease the likelihood of this complication&lt;br&gt;Avoid oversizing, overballooning</td>
</tr>
<tr>
<td>(2) Aortic dissection or rupture</td>
<td>Surgical control will likely be necessary, although this scenario is often lethal</td>
<td>Causes range from RV wire perforation to LV wire perforation, to aortic or LV rupture</td>
</tr>
<tr>
<td>(3) Pericardial tamponade</td>
<td>Percutaneous angioplasty may occasionally be of benefit&lt;br&gt;Surgical conversion is often necessary</td>
<td>Components of valve, or, more likely, a bulky leaflet atheroma may overlie and occlude a coronary os&lt;br&gt;Usually due to “frozen leaflet”</td>
</tr>
<tr>
<td>(4) Coronary ostial obstruction</td>
<td>A second transcatheter valve may need to be delivered&lt;br&gt;Surgical conversion may be necessary</td>
<td>Late pseudoaneurysm may result</td>
</tr>
<tr>
<td>(5) Acute severe aortic insufficiency</td>
<td>Surgical control&lt;br&gt;Individualized</td>
<td>From chordal tear during antegrade apical approach</td>
</tr>
<tr>
<td>Apical access site problems</td>
<td>Surgical control&lt;br&gt;Individualized</td>
<td>From chordal tear during antegrade apical approach</td>
</tr>
<tr>
<td>Internal cardiac tears (VSD or LV to LA fistula)</td>
<td>Surgery may be required</td>
<td>From chordal tear during antegrade apical approach</td>
</tr>
<tr>
<td>Acute mitral insufficiency</td>
<td>Individualized</td>
<td>From chordal tear during antegrade apical approach</td>
</tr>
<tr>
<td>Positioning and deployment problems</td>
<td>Multifactorial</td>
<td>From chordal tear during antegrade apical approach</td>
</tr>
<tr>
<td>Stroke</td>
<td>Multifactorial</td>
<td>From chordal tear during antegrade apical approach</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>Close monitoring&lt;br&gt;Pacemaker as needed</td>
<td>More commonly noted with Medtronic CoreValve device</td>
</tr>
<tr>
<td>Conduction disturbances</td>
<td>Fluid administration</td>
<td>More commonly noted with Medtronic CoreValve device</td>
</tr>
<tr>
<td>Suicidal LV</td>
<td>Fluid administration</td>
<td>More commonly noted with Medtronic CoreValve device</td>
</tr>
</tbody>
</table>

VSD, ventricular septal defect; LV, left ventricle (ventricular); LA, left atrium.
the best method to avoid perforation of the LV. Right heart perforation by the transvenous pacemaker is also possible [14].

**Coronary Ostial Obstruction**

Coronary obstruction may occur if an obstructive portion of the valve frame, or the sealing cuff, is placed directly over a coronary ostium; however, this is exceedingly rare. The presence of open cells over a coronary ostium is well tolerated. Although percutaneous coronary interventions have been performed successfully after valve implantation, it is likely that frame struts will prevent or complicate selective coronary cannulation.

A greater concern is the possibility of displacing an unusually bulky, calcified native leaflet over a coronary ostium. The diagnosis of coronary ostial obstruction may be reflected in the EKG trace or via sudden depression in left ventricular function on the echocardiogram. The echo may actually demonstrate the displacement of a calcified leaflet onto the coronary os.

Although acute coronary ostial obstruction may well prove fatal, some cases have been successfully managed by immediate percutaneous angioplasty or open bypass surgery. The risk of coronary occlusion is low, but difficult to assess, and most likely depends on the bulkiness of the native leaflets, height of the coronary ostia, and dimensions of the sinus of Valsalva.

**Acute Severe Aortic Insufficiency**

Acute severe aortic insufficiency after TAVR may produce hypotension and shock. Diagnosis may be suggested by hypotension and a wide pulse pressure on the arterial trace, with failure to maintain a good diastolic pressure after TAVR.

Significant transvalvular regurgitation is rare after TAVR, and is usually related to acute structural valve failure. This may include prosthesis rupture or malfunctioning leaflet (“frozen leaflet”), which is rare but, nevertheless, a possible complication after TAVR. Deployment of a second valve may be necessary. Alternatively, prompt cardiopulmonary bypass and surgical valve replacement may be required to sort out the problem (see below for a discussion of less severe paravalvular aortic regurgitation).

**Other Potential Technical Problems**

**Apical Access Issues**

Direct access to the left ventricular apex is achieved through an anterior mini-thoracotomy. The most common concern is chest wall discomfort with the associated potential for respiratory compromise and prolonged ventilation. Identifying the cardiac apex with transthoracic echo or fluoroscopy in two dimensions allows more direct access without the need for rib spreading other than by a soft tissue retractor [13].

On completion of the procedure, the apex is repaired with preinserted pledgeted sutures. A short burst of rapid ventricular pacing (rate between 130 and 140) is used to decrease LV systolic pressure during tying of these sutures. Postprocedural low-grade bleeding from the access site may result in cardiac tamponade and require further repair and prophylactic use of a biological glue. A pericardial patch cover can reduce this risk. Management of large tears might require institution of cardiopulmonary support [12].

Delayed pseudoaneurysm formation at the site of ventricular repair has been reported. Although pseudoaneurysms might be initially asymptomatic, they are typically progressive and require surgical intervention.

**Internal Cardiac Tears**

A tear created at the level of the valve inflow can result in either ventricular septal defect or a LV to left atrial shunt.

**Mitral Valve Injury**

During an antegrade apical approach, a wire can be passed below a mitral chorda, leading to distortion or avulsion of the mitral chordae. This may cause acute mitral regurgitation. Resistance to catheter advancement through the ventricle or transient mitral regurgitation assessed by transesophageal echocardiography should alert the operator to this possibility. Rewiring or use of a balloon flotation catheter may be considered to avoid subchordal passage [15].

Surgical treatment may be required if the mitral regurgitation is acute and severe.
Positioning and Deployment Problems

Improper Positioning
A valve extending excessively into the ventricle or the aorta may be associated with adverse events such as mitral insufficiency, arrhythmia, or aortic injury.

Prosthesis embolization immediately after deployment is generally the result of a gross error in positioning or ejection of the device by an effective ventricular contraction during deployment.

Embolization to the aorta is well tolerated so long as coaxial wire position is maintained, preventing the valve from flipping over and obstructing the antegrade flow. Typically, the valve can be snared or repositioned with a partially inflated valvuloplasty balloon into a stable position in the aorta. A TAVR reattempt is often successful, although an alternative approach might be advisable when the reason for initial failure cannot be identified. Embolization to the LV is far less likely, but in such cases, surgical removal might be the only option available.

Paravalvular regurgitation, due to incomplete annular sealing, is common. Some degree of paravalvular aortic regurgitation is reported in 80-96% of cases. In most cases, the degree of regurgitation is trivial or mild. Grade 2+ regurgitation is found in 7-24% of patients. Although no trial has directly compared the Edwards SAPIEN and Medtronic CoreValve devices, the rates of regurgitation reported in the literature seem to be similar for the two devices. Appropriate sizing with multiple imaging modalities is one way of reducing this problem, which adversely impacts long-term survival. Sometimes further ballooning may reduce or abolish the aortic regurgitation.

Paravalvular Regurgitation
Mild to moderate paravalvular regurgitation usually does not produce severe, acute hemodynamic derangement. During follow-up, regurgitation is more often reduced, rather than becoming worse. The importance of paravalvular leak has been emphasized in several reports in which grade ≥2+ regurgitation has been shown to be an independent predictor of short- and long-term survival [16].

Stroke
Neurological events are generally multifactorial, with some related to the procedure. Manipulation of a wire and/or large-diameter catheter through the aortic arch, positioning of the device, performance of balloon aortic valvuloplasty, and inadequate blood flow to the brain during rapid pacing and device deployment are all potential causes of neurologic injury. Factors related to the very elderly patient substrates, in whom the incidence of atrial fibrillation and atherosclerotic disease is high, contribute to the risk of peri-procedural cerebrovascular events. Reported incidence of clinical stroke in the current literature varies between 1.7% and 8.4% [17].

Initially, it was anticipated that stroke associated with TAVR occurred during the procedure, but in-depth analysis of this issue has demonstrated a continuous hazard extending beyond the early phase. This hazard was thought to be higher after Transcatheter aortic valve implantation (TAVI) in comparison with surgical aortic valve replacement (SAVR). However, recent data have shown that although the difference is significant in the first 30 days, the late hazard is in fact similar between TAVI and SAVR.

The role of atrial fibrillation as a potential mechanism for stroke after TAVI has been emphasized in two recent reports, which show a fourfold increased risk of stroke.

There are several embolic protection devices currently under investigation. Reports have not shown a clinical impact on reducing the incidence of overt or silent neurological events after TAVR.

Acute Kidney Injury
The incidence of acute kidney injury (AKI), according to multiple reports, lies around 7-8%. Many of these studies have been consistent in identifying blood transfusion as a predictor of AKI. Transfusions are most likely related to bleeding resulting from the vascular access site. The dye load certainly contributes to kidney injury. Predisposing factors include hypertension, chronic obstructive pulmonary disease, and abnormal baseline renal function. Toggweller S. et al. reported that TAVR patients who had AKI had significantly higher in-hospital mortality and worse long-term survival [18,19].

Conduction Disturbances
It has now been identified that the self-expandable Medtronic CoreValve system (because of the higher and longer-lasting radial forces as well as the deeper implantation site in the left ventricle outflow tract) has a higher rate of pacemaker requirement than the Edwards SAPIEN
system. The incidence is higher in patients who have a left or right bundle branch block prior to implantation.

A recent meta-analysis reported that 28.9% (23-36%) of patients implanted with the Medtronic CoreValve valve and 4.9% (4-6%) of patients implanted with the Edwards SAPIEN valve will require a new permanent pacemaker [19].

Given the variable timing of the possible occurrence of high-degree AV block, continuous postprocedural ECG monitoring should be performed for at least 72 hours for those patients considered to be at increased risk for this complication. Avoiding over-sizing and deep implantation in the outflow tract can reduce the incidence of this complication [19].

The “Suicidal LV”

In rare circumstances, after sudden reversal of chronic, severe aortic stenosis, the sudden disappearance of afterload can permit the hypertrophied left ventricle to contract so forcefully and completely that it obstructs forward flow. The subvalvular hypertrophy obstructs outflow from the LV. This has been eloquently termed the “suicidal LV” post-TAVR.

Treatment involves fluid administration and avoidance of diuretics.

Conclusion

TAVR has become the standard of care for those patients for whom the surgical risk is deemed prohibitive. TAVR is also emerging as a reasonable alternative for those selected, operable patients in whom the risk of either mortality or morbidity is “high.” Although bleeding and vascular complications are decreasing as TAVR technology improves and continues to miniaturize, significant and potentially catastrophic mechanical complications may still occur. Having a clear, focused, prepared outlook to the recognition and treatment of these TAVR-related catastrophes is essential for the care team. This article has provided a framework for such a perspective.

Conflict of Interest

Adam El-Gamel is a proctor and consultant for Edwards Life Science.

References


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EDITOR’S COMMENTS AND QUESTIONS:

Editor’s Comments:
This excellent article by Dr. El-Gamel provides a clear diagnostic and therapeutic approach for catastrophic complications, which can occur during or immediately after TAVI. Having this clear diagnostic and therapeutic map in mind is likely to save lives. This article is recommended for all teams starting or performing TAVI.

Editor’s Questions:
As the indication for TAVI has classified the patients into two different groups—the first being the inoperable AS patients and the second group being the high-risk operable surgical patients, the team has to make an individual call before the procedure if surgical intervention has a place in an individual patient; it makes no sense to perform an emergency procedure on a patient who was rejected for an elective operation (inoperable patient). It is imperative that the Heart Team, the patient, and the patient’s family are aware of the limit to the extent of surgery that will be offered in the event of a significant complication. For example, we feel that redo sternotomy and repair of a type A dissection in a nonagenarian is inappropriate and would not be undertaken. Prevention of complications required during TAVI appears to be of critical importance. As the outcome of emergency surgical intervention offers poor outcome, this should be discussed at length with all parties and then documented in the patient’s file prior to the procedure.

1. Is it worth operating for rupture of the aortic root from TAVI? Is there any meaningful chance of salvage?

Reported 30-day mortality of TAVI complications needing surgical intervention from the European source registry was high (51.9%) and showed cause-specific differences, with 100% mortality in patients with aortic rupture or cardiac tamponade, 0% death in those with acute aortic regurgitation, and intermediate risk of death or intermediate mortality risk in those with aortic injury or valve embolization/migration. So the experience and data do not support surgery for aortic or cardiac rupture.

2. Is it worth operating for non-ruptured aortic dissection occurring during TAVI?

The decision to operate on acute dissection is complicated by the patient characteristics, previous operation, and age. For example, we feel that redo sternotomy and repair of a type A dissection in a nonagenarian is inappropriate and would not be undertaken. However, an 80-year-old with no previous history of cardiac surgery, considered operable but high risk for conventional surgery, may be offered surgical repair.

3. Is it worth operating for coronary ostial occlusion occurring during TAVI?

Operating for coronary occlusion and aortic incompetence has the best outcomes, so surgery should be offered in the operable patients who are accepted for TAVI.
Esophago-Pleural Fistula Caused by Compression Necrosis In a Patient With Acute Type B Aortic Dissection

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Abstract
Esophago-pleural fistula associated with thoracic aortic aneurysm is a rare and lethal complication. We report the case of a 62-year-old male who suffered from esophago-pleural fistula 56 days after thoracoabdominal aortic surgery. Contrast CT showed that the fistula occurred at the level of the esophagus compressed by rapid dilatation of thoracic aorta and endoscopy revealed no ischemic signs on esophageal mucosa, demonstrating that the cause of esophago-pleural fistula was compression necrosis due to rapid dilatation of the thoracoabdominal aortic aneurysm.

Key Words
Esophago-pleural fistula · Acute aortic dissection · Complication

Introduction
A 62-year-old male with a history of hypertension presented to the hospital with sudden onset of back pain and paraplegia. Contrast computed tomography (CT) demonstrated Stanford type B acute aortic dissection with triple barrel of the thoracoabdominal aorta, in which the maximal diameter was 60 mm (Fig. 1). Open repair was considered for prevention of rupture, but his respiratory condition was severely poor in addition to complete paraplegia; hence, conservative treatment was selected. CT at 10 days after the onset of dissection revealed rapid dilatation of the thoracoabdominal aortic aneurysm, in which the maximal diameter reached 105 mm with compression of the esophagus (Fig. 2). Graft replacement of the thoracoabdominal aortic aneurysm was emergently performed. During the operation, proximal anastomosis was made just below the left subclavian artery with-

Figure 1. Contrast computed tomography (CT) on admission demonstrated Stanford type B acute aortic dissection with 60 mm maximal diameter.
out aortic clamping under deep hypothermic circulatory arrest. Distal anastomosis was made just above the renal arteries in the retroperitoneal space. Reconstruction of the intercostal arteries was not done because of preoperative paraplegia. Although left recurrent laryngeal nerve paralysis occurred as a complication, the operation was successful. The patient underwent rehabilitation up until discharge while on nasal tube feeding. At 39 days postoperatively, spiking fever occurred a few times per day. White blood cell count and C-reactive protein level were $7500 \times 10^3/\mu L$ and 9.97 mg/dL, respectively. *Pseudomonas aeruginosa* was cultured from blood, but there was no obvious focus of infection identified on CT. Antibiotic treatment was initiated, and spiking fever gradually abated. Antibiotic treatment was continued for prophylaxis of graft infection. At 56 days postoperatively, contrasted CT as part of periodic inspection revealed pleural abscess around the vascular prosthesis, and perforation of the esophagus was suspected (Fig. 3). Endoscopy demonstrated the vascular prosthesis through a large esophago-pleural fistula (Fig. 4). The patient underwent emergent video-assisted thoracoscopic esophagectomy and thoracic drainage. Cervical salivary fistula was then established by use of the oral end of the esophagus, and an enteral feeding tube was placed in the jejunum. After the operation, intrathoracic irrigation from the thoracic tube was performed and antibiotic treatment was maintained. However, *Pseudomonas aeruginosa* was again detected in the culture of thoracic drainage. We recommended performing a graft replacement of the infected vascular prosthesis with omental plombage, but his family did not consent. He suffered from sepsis due to infection of the vascular prosthesis and died at 4 months after the surgery.
This case is our experience of a large esophago-pleural fistula in a patient with acute Type B aortic dissection. The causes of the esophago-pleural fistula were not believed to be due to surgical trauma during the operation or mechanical stimulation of the vascular prosthesis. Surgical procedures which could induce damage to the esophagus, such as resection of the aortic wall, aortic clamping, and reconstruction of the intercostal arteries, were not performed, and the vascular prosthesis was not in contact with the fistula as demonstrated by postoperative CT. Esophageal ischemia due to malperfusion may have influenced the perforation of the esophagus. However, endoscopy did not show necrotic or ulcerated esophageal mucosa around the fistula. Therefore, it is considered that the cause of the esophago-pleural fistula was the compression necrosis due to rapid dilatation of the thoracoabdominal aortic aneurysm. A small esophago-pleural fistula occurred on the 39th postoperative day when spiking fever appeared. However, it was discovered only after the fistula became large because infection was controlled initially by nasal tube feeding and appropriate antibiotic treatment.

Comment on this Article or Ask a Question

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EDITOR’S QUESTIONS

1. Did you consider intervening initially with fenestration or endograft to try to reverse the paraplegia?

No, I didn’t. Actually, when he was admitted to our hospital, 8 hours had passed since the paraplegia had occurred. Then, cerebrospinal fluid drainage was performed for 72 hours, but the paraplegia was not recovered.

2. You intervened at ten days to replace the aorta, so the native aorta was then "depressurized". How, then, could the aortic wall produce pressure to result in esophageal necrosis?

There are some possibilities that could cause perforation of the esophagus such as rupture of the aneurysm to the esophagus, surgical trauma during the operation, esophageal necrosis due to malperfusion, or compression necrosis due to rapid dilatation of the aneurysm. During the operation, there were no signs of aneurysmal rupture. On the other hand, any surgical procedure which could induce damage to the esophagus, such as resection of the aortic wall, aortic clamping, and reconstruction of the intercostal arteries, was not performed. Therefore, it is not considered that the cause of esophageal perforation was the rupture to the esophagus from the surgical trauma. It is possible that esophageal ischemia due to malperfusion may have influenced the perforation of the esophagus because the intrathoracic esophagus is mainly supplied by the intercostal arteries which were occluded by the thrombosed false lumen of aortic dissection. However, endoscopy did not show necrotic or ulcerated esophageal mucosa around the fistula. Therefore, it is considered that the cause of esophageal perforation was the compression necrosis due to rapid dilatation of the thoracoabdominal aortic aneurysm.
Finger-Thumb Technique for Elephant Trunk Retrieval

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Abstract
In this report we present a brief video illustrating the “Finger-Thumb Technique” that we have used extensively at our institution for elephant trunk retrieval during second stage elephant trunk procedures. Although only safe in experienced hands, this technique is a viable option in the arsenal of a cardiothoracic surgeon, especially in cases when proximally surrounding a massively enlarged aorta is unappealing.

Key Words
Descending aorta · Thoracic aortic aneurysm · Surgical treatment · Stage II elephant trunk procedure

Staged open surgical treatment of aneurysms of the aortic arch and descending aorta was first described by Borst [1], and then modified by Crawford [2] and Svensson [3]. The essence of the two-stage procedure is in the “elephant trunk” graft that is inserted into the descending aorta during arch replacement surgery. The elephant trunk graft is left hanging in the lumen of the descending aorta in anticipation of the second stage intervention (performed usually a few weeks or months later), during which another graft will be attached to this elephant trunk. Anastomosing the descending aortic graft to the preplaced elephant trunk is often preferable to anastomosing to a dilated distal aortic arch under deep hypothermic arrest. Identifying and retrieving the elephant trunk graft safely during the second stage intervention is key to making this operation successful, perhaps its most critical step. Retrieval of the elephant trunk for performance of a Stage II procedure is not trivial, especially because the elephant trunk is often left short, in order to discourage paraplegia due to coverage of many pairs of intercostal arteries. Often the elephant trunk terminates just beyond the aortic arch.

There are several technical options for elephant trunk retrieval:

1. The aorta and the contained elephant trunk can be surrounded above the terminus of the elephant trunk as described previously [3]. However, this is not entirely benign, as the aorta may be very large at that level and there will be local inflammation from the Stage I procedure. Aortic, esophageal, or recurrent laryngeal injury may be incurred.

2. A second alternative is that the entire procedure may be done under deep hypothermic circulatory arrest (DHCA), but that defeats the rationale of the elephant trunk procedure, which is meant to facilitate conduct of Stage II. Once the elephant trunk is safely controlled, there is no need for any DHCA.

3. A third alternative is to use high-dose adenosine [4,5] (or rapid ventricular pacing) to produce transient cardiac standstill, during which the aorta may be opened without exsanguination.

4. The Finger-Thumb technique.

In this report we present the fourth alternative, illustrated in this brief video (http://dx.doi.org/10.12945/j.aorta.2013.13.064.vid.01). We call this technique the “Finger-Thumb” technique. As the name implies, the index finger and the thumb enter the...
Figure 1. Illustrated is the transesophageal echocardiography-guided approach to the elephant trunk graft. Please note the location of the recurrent laryngeal nerve, which can be injured while encircling the proximal descending aorta.

Figure 2. Schematic illustration of elephant trunk graft retrieval in preparation for clamping.

Figure 3. Intraoperative transesophageal echocardiography image showing the elephant trunk graft (indicated by red arrow) in the lumen of the descending aorta. Transesophageal and direct epi-aortic echocardiography confirm appropriate location of the incision for the Finger-Thumb technique.
descending aorta via a small vertical incision on the aorta and locate and retrieve the elephant trunk graft by direct palpation (Fig. 1 and Fig. 2). We always identify the end of the elephant trunk by intraoperative transesophageal and epi-aortic echocardiography (Fig. 1 and Fig. 3), so that an incision in the aorta can be made at the ideal level.

Here are a few practical tips that we would like to share:

- There is no margin for error, as the patient can exsanguinate in seconds if this procedure goes awry.
- The graft may adhere to the wall of the aorta, making identification and retrieval more difficult. It can be teased away during Finger-Thumb retrieval process.
- In dissection cases, one must be certain to explore for the graft in the true lumen (the aorta will have been fenestrated as far as possible during Stage I).
- When the aorta is ultimately opened after control of the elephant trunk, high intercostal arteries may be hard to identify if they originate at the top of the elephant trunk.

In conclusion, we believe that the “Finger-Thumb” is an extremely useful technique for elephant trunk retrieval during a second stage procedure. Although only safe in experienced hands, this technique is a viable option in the arsenal of a cardiothoracic surgeon, especially in cases when proximally surrounding a massively enlarged aorta is unappealing.

Comment on this Article or Ask a Question

References


Upcoming Meetings

February 2014

1. 43rd Annual Meeting of the German Society for Thoracic and Cardiovascular Surgery
   February 9–12, 2014
   Messe Freiburg, Germany
   Meeting information available at: www.dgthg-jahrestagung.de/

March 2014

1. Aortic Valve Repair: A Step by Step Approach
   March 6–7, 2014
   Paris, France
   Meeting information available at: www.caviaar.com

2. The Houston Aortic Symposium: Frontiers in Cardiovascular Diseases, the Seventh in the Series
   March 6–8, 2014
   Houston, Texas
   Meeting information available at: www.promedicacme.com

3. Advanced Module: Open and Endovascular Aortic Therapy
   March 19–21, 2014
   Windsor, United Kingdom
   Meeting information available at: www.eacts.org/academy/2014-program/

April 2014

1. American Association for Thoracic Surgery Aortic Symposium
   April 24–25, 2014
   New York, New York
   Meeting information available at: www.aats.org/aortic

   April 26–30, 2014
   Toronto, Canada
   Meeting information available at: www.aats.org/annualmeeting/

3. 61st Annual Conference of the Israel Heart Society
   April 30–May 1, 2014
   Tel-Aviv, Israel
   Meeting information available at: http://en.israelheart.com/