Prediction of the future risk of endoleak complications based on statistical method

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Introduction

Statistical methods have been widely used in the medical fields, however it has been mainly focused on the effectiveness of the drug or the treatment. On the other hand, in spite of recent remarkable development of medical imager, doctors have been entirely making a visual assessment using the medical imaging, and it usually depends on the experience of them. Recently, in addition to the traditional visual image assessment, various methods of image assessment based on quantitative parameters has been required. Among them, a method of objective assessment for multiple parameters obtained through images has been attracting attention.

Aneurysm is a disease that shows enlargement of aorta associated with aging and atherosclerotic change. Patients with aneurysm pose fatal risk of aortic rupture and need appropriate treatment. For many years, surgical treatment is the standard treatment of aneurysm reducing mortality of the patients. Thoracic endovascular aortic repair (TEVAR) is a new optional treatment for aortic aneurysm. TEVAR is a minimally invasive procedure in which a stent graft is inserted through the femoral artery and expanded at the site of the aneurysm. Once in place, the stent creates a new path for blood flow, reducing pressure on the aneurysm and the risk of rupture. The US Food and Drug Administration (FDA) approved the first commercially available stent graft in 2005, and since then TEVAR has become widely accepted as the primary option for the treatment of multiple thoracic aortic diseases. And now, the concern with TEVAR as an alternate treatment of surgical repair has been growing. Makaroun MS et al. (2008) compared the results of TEVAR and surgical repair performed between 1999 and 2003 in patients with descending thoracic aortic aneurysms. The comparison showed no significant differences for total mortality, while TEVAR exhibited significantly lower incidences of aneurysm-related mortality and major adverse events.

One complication of TEVAR is an endoleak, a leakage of blood into the aneurysm sac after endovascular repair, and it occurs in 4% to 29% of patients. Although many researchers have empirically recognized that the cause of endoleaks is the aortic morphology, the specific relationship between aortic curvature and the risk of endoleaks after TEVAR has not been quantitatively defined. In this study, we constructed a discriminant model to predict endoleak occurrence after TEVAR using quantitative variables computed on the basis of CT angiography. In addition, we examined the reliability of the discriminant model using variable selection and cross validation.

Materials

Between April 2001 and September 2008, 121 consecutive patients were prospectively enrolled in one of the six FDA-sponsored clinical trials examining the Thoracic Excluder or TAG stent-graft devices (W.L. Gore & Assocs., Flagstaff, AZ). Among them, we excluded the cases having complex aortic morphology and different mechanisms. We also excluded patients for whom pre-procedural CT angiography was not available or was of poor quality. As a result, a total of 40 patients (28 men, 12 women) having a mean age of 74 years (range, 40-89 years) were included in this study. Among these, 17 did not have any endoleaks and 23 had one or two endoleaks. Although many researchers have reported that the tortuosity of the aortic arch may independently affect the risk of endoleak occurrence, the relationship between aortic morphology and endoleaks is not yet fully understood. One reason is the difficulty associated with making objective assessments of the aortic morphology. In this study, we defined a curvature index $\kappa = 1/D\,\mathrm{cm}^{-1}$ that quantifies the aortic morphology (Rubin GD et el.,1998). The mean diameter (D) and the curvature (κ) of the aortic flow lumen are calculated at 1-mm increments along the median luminal centreline computed based on CT angiography (Figure 1).

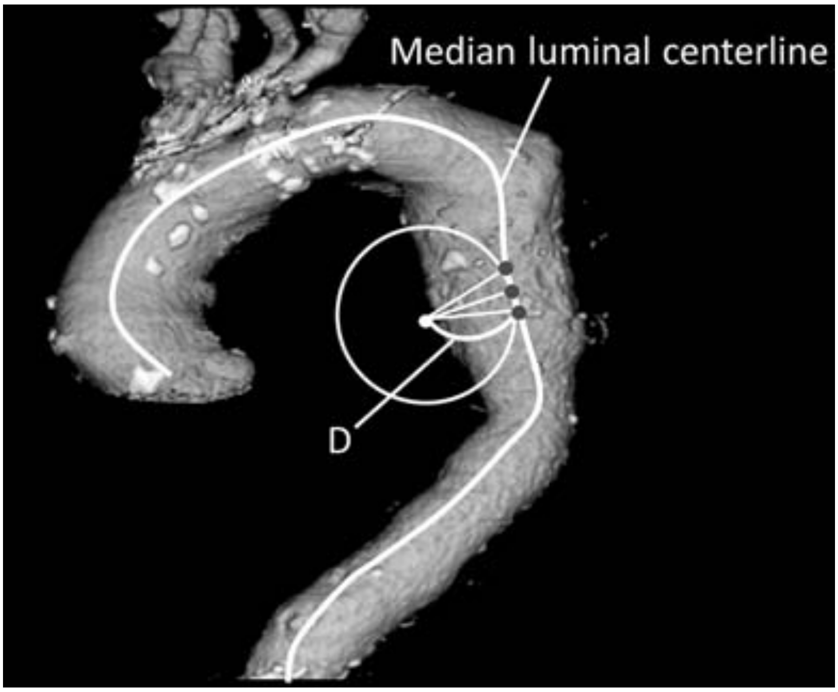

Figure 1: Pre-procedural volume-rendered 3D-CT angiographic image.

In order to standardize the aorta length, the lengths from all cases were normalized, and the aorta was divided into 14 segments (Seg1-Seg14). Figure 2 illustrates the mean and standard deviation of the κ at each segment and whether or not they are separated by endoleaks. The ‘no endoleak’ group showed a maximum curvature index of $0.29\,\mathrm{cm}^{-1}$ at Seg4, which corresponded to a sharp curve in the aortic arch. The ‘endoleak’ group showed a large curvature index exceeding $0.15\,\mathrm{cm}^{-1}$ for Seg1-Seg9, indicating that there is a constantly large curvature index throughout the aortic arch.

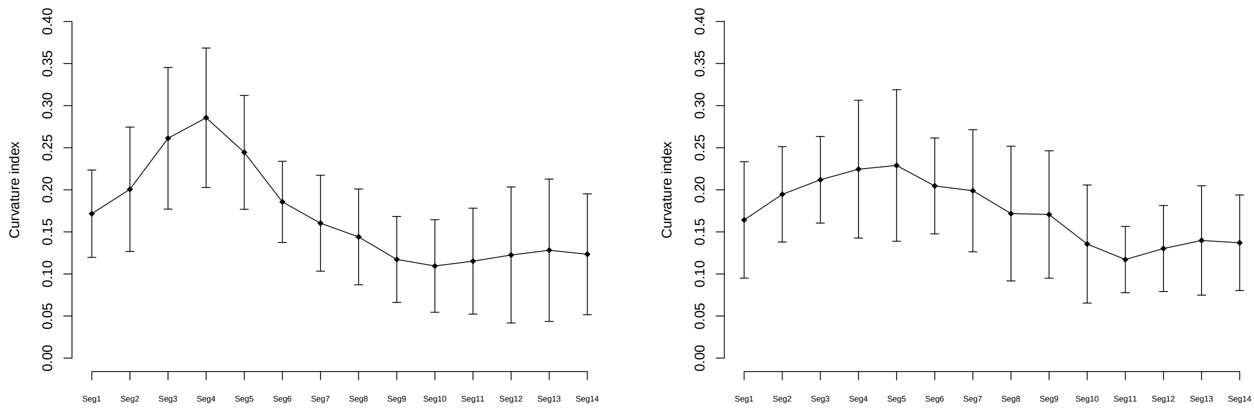

Figure 2: Graphs of the mean curvature index (κ) and standard deviation calculated for each segment of patients in both groups: ‘no-endoleak’ group (left) and ‘endoleak’ group (right).

Discriminant analysis for prediction of endoleak

The mean curavature (κ) of each segment is calculated as the explanatory variables. The **length** between the proximal neck and the distal neck is an independent parameter of aneurysm length in each case. **Pneck** and **Dneck** are defined as the dummy variables of disease location (**Pneck**= 1 when the position of the proximal neck is located in the proximal half of the entire aorta, or otherwise **Pneck**= 0; **Dneck**= 1 when the position of the distal neck is located in the distal half of the entire aorta, or otherwise **Dneck**= 0). We first examined whether there are any significant differences between both groups for each of the independent variables using analysis of variance. If significant differences were absent, further analysis was not necessary. Table 1 shows the equality tests of group means for each variable. It provides statistical evidence for the significant differences that exist between both groups for some variables.

Table 1: Equality of group means for each variable.

	F	p Value		F	p Value
Seg1	.137	.714	**Seg10**	1.611	.212
Seg2	.085	.772	**Seg11**	.014	.905
Seg3	5.258	.027	**Seg12**	.136	.714
Seg4	5.394	.026	**Seg13**	.242	.625
Seg5	.359	.553	**Seg14**	.449	.507
Seg6	1.230	.274	**Length**	3.873	.056
Seg7	3.302	.077	**Pneck**	4.682	.037
Seg8	1.484	.231	**Dneck**	.721	.401
Seg9	6.312	.016			

In this study, we constructed a model using the forward stepwise selection method. Table 2 shows the addition or removal of variations for each variable based on F criteria using the stepwise method in all 14 explanatory variables, and the accuracy of each model. In addition, we applied the leave-one-out cross-validation technique for evaluating the construction of each model. Based on the accuracy of each model and accuracy of cross validation in Table 2, we observed that the model selected by eight variables was considered to be valid. The explanatory variables from Table 2 that were used are as follows: '**Seg4**', '**Seg6**', '**Seg7**', '**Seg8**', '**Seg9**', '**Seg10**', '**Pneck**' and '**Dneck**'. Here the Wilks's λ which indicates the significance of the discriminant function, is 0.568, and its p value is 0.001. The canonical discriminant function coefficients are shown in Table 3.

Table 2: Explanatory variables obtained by stepwise selection.

F_{in}	0	1	2	3
F_{out}	0	0.5	1	1.5
Explanatory variables	17	8	5	2
Seg1	○			
Seg2	○			
Seg3	○			
Seg4	○	○	○	
Seg5	○			
Seg6	○	○	○	
Seg7	○	○		
Seg8	○	○		
Seg9	○	○	○	○
Seg10	○	○		
Seg11	○			
Seg12	○			
Seg13	○			
Seg14	○			
Length	○			
Pneck	○	○	○	○
Dneck	○	○	○	
Accuracy	0.925	0.900	0.825	0.750
Accuracy of cross validation	0.675	0.825	0.800	0.750

Table 3: Canonical discriminant function coefficients

	Coefficients
Seg4	0.092
Seg6	−0.059
Seg7	−0.153
Seg8	0.262
Seg9	−0.284
Seg10	0.121
Pneck	−1.835
Dneck	1.063
(Constant)	1.654

Table 4 summarizes the results of the risk of endoleaks obtained by discriminant analysis using eight variables. None of the observed endoleaks were misclassified as belonging to the no-risk group. In contrast, four cases having no observed endoleaks were misclassified as belonging to the risk group.

Misclassifications based on curvature indices did not exhibit any recognizable patterns or tendencies. The sensitivity, specificity and accuracy with which endoleaks were predicted were 100.0%, 76.5% and 90.0%, respectively. Moreover, the likelihood ratio for a negative finding ($LR(-)$), which is an indicator of the occurrence of negative tests in patients [$LR(-) = (1-sensitivity)/specificity$], found to be 0. For sufficiently low $LR(-)$ (< 0.1), the discriminant model based on the curvature index is effective for exclusion diagnosis. Table 5 summarizes the results of cross validation. The results indicate that the accuracy is 82.5%, and particularly, the endoleak(+) diagnosis could get a high reliability of 91.3%.

Table 4: Predictive matrix for the presence of endoleaks obtained from discriminant analysis.

	Observed endoleak		
	Endoleak(−)	Endoleak(+)	Total
Predicted endoleak			
Endoleak(−)	13	0	13
Endoleak(+)	4	23	27
Total	17	23	40

Table 5: Result of cross validation.

	Observed endoleak		
	Endoleak(−)	Endoleak(+)	Total
Predicted endoleak			
Endoleak(−)	12	2	14
Endoleak(+)	5	21	26
Total	17	23	40

Conclusion

In this study, we evaluated endoleak occurrence by quantitative assessment of the curvature based on aortic morphology by discriminant analysis. In addition, the reliability of the model was examined using variable selection and cross validation. The discriminant model was validated by its accurate prediction of the risk of endoleaks and had a sensitivity of 100% and a specificity of 76.5%. With few exceptions, the evaluation of aortic morphology using discriminant analysis has proven to be a reliable method for predicting the potential risk of future endoleaks. However, this study only evaluated the relationship between endoleaks and aortic curvature. Other potential contributing parameters, such as aortic diameter and length and number of stent grafts, were not assessed in this study. In summary, native thoracic aortic morphology is a significant factor in the prediction of endoleaks after TEVAR. Discriminant analysis of native thoracic aortic morphology from CT angiography is useful to predict the risk of endoleaks, and may be incorporated into pre-procedural planning and post-procedural surveillance protocols.

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