タイトル	Evaluation of Morphological Dynamic Changes in the Aortic Annulus and Sinotubular Junction in Candidate Patients for Transcatheter Aortic Valve Implantation Using 4-Dimensional Computed Tomography Voxel Tracking
作成者（著者）	Sakai, Kota / Iguchi, Nobuo / Tamura, Harutoshi / Utanohara, Yuko / Isobe, Mitsuaki / Ikeda, Takanori
公開者	The Medical Society of Toho University
発行日	2020.06.01
ISSN	21891990
掲載情報	Toho Journal of Medicine. 6(2). p.67-73.
資料種別	学術雑誌論文
内容記述	Original Article
著者版フラグ	publisher
JaLCDOI	info:doi/10.14994/tohojmed.2019-019
メタデータのＵＲＬ	https://mylibrary.toho-u.ac.jp/webopac/TD29440010

Original Article

Evaluation of Morphological Dynamic Changes in the Aortic Annulus and Sinotubular Junction in Candidate Patients for Transcatheter Aortic Valve Implantation Using 4-Dimensional Computed Tomography Voxel Tracking

Kota Sakai[1)] Nobuo Iguchi[2)]* Harutoshi Tamura[2)]
Yuko Utanohara[2)] Mitsuaki Isobe[2)] and Takanori Ikeda[1)]

[1)]Department of Cardiology, Toho University Graduate School of Medicine, Tokyo, Japan
[2)]Department of Cardiology, Sakakibara Heart Institute, Tokyo, Japan

ABSTRACT

Introduction: In recent years, rather than surgically replacing the aortic valve, transcatheter aortic valve implantation (TAVI) has been performed. This study aimed to evaluate the morphological dynamic changes in the aortic annulus and sinotubular junction (STJ) using 4D-computed tomography (CT) voxel tracking in TAVI candidates.

Methods: We enrolled 75 consecutive patients with aortic stenosis (AS) and 42 controls who underwent cardiac CT. Scans were performed using spiral acquisition with retrospective electrocardiogram-gated image reconstruction. We used motion coherence image processing, which performs deformable registration to track all voxels throughout multiple phases and interpolates images between phases to generate new phases. Using voxel tracking technology, we constructed a time-area curve and time-circumference length curve for the aortic annulus and STJ, respectively. From these curves, we determined the peak and nadir values of the area and circumference length during one cardiac cycle.

Results: There was no significant difference between the AS and control groups regarding the area size, but the circumference length was significantly greater in the AS group than in the controls ($p < 0.001$). The phase with the largest area was significantly slower in the AS group than in the controls ($p = 0.005$). In both groups, the changes in area and circumference length were greater in the aortic annulus than in the STJ ($p < 0.001$).

Conclusions: Dilatability during the cardiac cycle is different between the aortic annulus and the STJ. Additionally, the phase during which the aortic annulus area is maximum occurs later than normal in patients with AS.

Toho J Med 6 (2): 67–73, 2020

KEYWORDS: aortic annulus, STJ, 4D-CT, transcatheter aortic valve implantation (TAVI), voxel tracking

*Corresponding Author: Nobuo Iguchi, 3-16-1, Asahi-cho, Fuchu-city, Tokyo, 183-0003, Japan, tel: +81-042-314-3141
e-mail: niguchi@shi.heart.or.jp
DOI: 10.14994/tohojmed.2019-019

Received Sept. 26, 2019: Accepted Nov. 11, 2019
Toho Journal of Medicine 6 (2), June 1, 2020.
ISSN 2189-1990, CODEN: TJMOA2

1. Introduction

In recent years, transcatheter aortic valve implantation (TAVI) has been performed instead of surgical aortic valve replacement. The conditions that previously excluded older people and patients with certain systemic complications from being candidates for open heart surgery have been addressed by TAVI.[1, 2] Devices that are used for TAVI are also undergoing advances,[3] but they are not yet sufficient.[4] To create more sophisticated devices, morphological changes in the cardiac cycle of the aortic root must be accurately evaluated.[5, 6] In recent years, devices have been introduced that cover a longer area, from the aortic annulus to beyond the sinotubular junction (STJ). Thus, the dynamics of the aortic annulus and STJ must be accurately evaluated.[7] To date, however, there have been no reports that compared morphological dynamic changes in the aortic annulus and STJ using four-dimensional (4D) voxel tracking.

Although dynamic changes in the aortic annulus can be evaluated with three-dimensional (3D) echocardiography, true morphological change cannot be assessed—only visual and functional areas.[3] Hence, to accurately investigate morphological changes, techniques such as voxel tracking, which tracks the same point in motion, are necessary. A recently developed software called PhyZiodynamics is capable of voxel tracking in computed tomography (CT) images and can evaluate structural changes of the aorta in four dimensions.

The aortic annulus and STJ have different tissue properties,[8] and true morphological dynamic changes should be accurately evaluated by voxel tracking technology on 4D images. Furthermore, the phase at which the aortic annulus or STJ is maximum cannot be predicted, so obtaining a true maximum value without 4D imaging is impossible.

We therefore aimed to evaluate the morphological dynamic changes in the aortic annulus and STJ using 4D-CT with PhyZiodynamics software for TAVI candidates.

2. Methods

2.1. Study population

The study included 80 consecutive patients with aortic stenosis (AS) and 42 controls who underwent cardiac CT between October 2013 and March 2016. All patients with AS were candidates for TAVI and underwent cardiac CT to assess the aortic valve. Controls were chosen from among patients who underwent cardiac CT because of suspected coronary disease and who had normal left ventricular (LV) systolic function with no coronary disease, cardiomyopathy, valve disease, or severe hypertension.

The investigation conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the in-house ethics committee of Sakakibara Heart Institute (No. 16-040).

2.2. Cardiac CT image acquisition

All patients with AS and controls underwent cardiac CT using a dual-source CT system (SOMATOM Definition Flash; Siemens Healthcare, Forchheim, Germany). Each patient's electrocardiogram was prospectively monitored throughout the procedure. Beta-blockers were administered to all control patients as pretreatment for CT but not to the AS patients.

The appropriate time interval between contrast agent injection and scanning initiation was determined by a test injection of 7 mL of contrast agent. Scans were performed using spiral acquisition with retrospective electrocardiogram-gated image reconstruction during injection of iopamidol (370 mg I/mL) (Iopamiron 370; Bayer, Osaka, Japan), with a gantry rotation time of 280 ms. Scan parameters, such as tube current, tube voltage, and exposure dose, are shown in Table 1. Axial images were reconstructed with a slice thickness at 0.75-mm intervals using retrospective gating to obtain image acquisition windows of the full duration of the cardiac cycle. For each patient, 20 data sets were created at different time points during the cardiac cycle (0%-95% of the R-R interval).

2.3. Image reconstruction with motion coherence image processing and analysis

On cross sections of the virtual basal ring and the STJ, we traced the cross-sectional images to coincide with the full width at half maximum of the CT values.[9] We examined the following parameters of the aortic annulus and STJ: area, circumference length, minor axis diameter, major axis diameter.

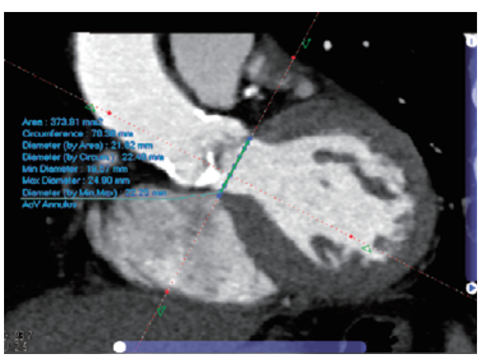
Motion coherence image processing is a novel technique (PhyZiodynamics; Ziosoft Inc., Tokyo, Japan) that performs deformable registration to track all the voxels throughout multiple phases and interpolates images between phases to generate new phases.[10] Using voxel tracking technology, noise reduction and interpolation of the volume data of 20-40 phases were performed automatically (Fig. 1). Time-area and time-circumference curves were constructed (Fig. 2). From these curves, we determined the

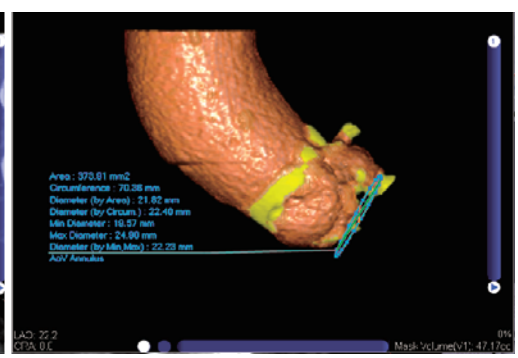
Table 1 Patient baseline characteristics

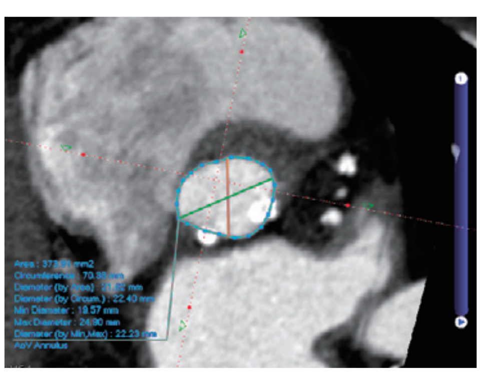
	Control group (n = 42)	Patients with severe AS (n = 75)
Age, years	64 ± 13	83 ± 7
Male	28 (67%)	19 (25%)
Hypertension	20 (48%)	57 (76%)
Dyslipidemia	10 (24%)	44 (59%)
Diabetes	3 (7%)	21 (28%)
Chronic kidney disease	0 (0%)	40 (53%)
Ischemic heart disease	0 (0%)	29 (39%)
Old cerebral infarction	1 (2%)	15 (20%)
Echo findings		
AVA (cm2)		0.58 ± 0.16
Mean PG (mmHg)		58.1 ± 15.8
Peak flow velocity (m/s)		5.0 ± 0.7
CT examination		
Tube voltages (kV)	117.62 ± 6.48	109.07 ± 9.96
Tube current (mAs)	383.29 ± 57.87	352.00 ± 56.14
CT dose indices	113.82 ± 22.66	88.60 ± 31.24
Dose length product	1890.36 ± 437.19	1369.65 ± 490.17

Values are mean ± SD or n (%)

AS = aortic stenosis, PG = pressure gradient, AVA = aortic valve area


MPR image of long axis view


Volume-rendering image


MPR image of short axis view

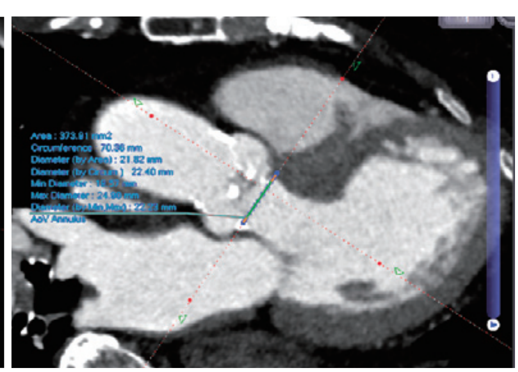

MPR image of two-chamber view

Fig. 1 Measurement of the aortic annulus. On the virtual aortic annulus surface, we traced cross-sectional images to coincide with the full width at half maximum of CT values. Forty phase images were automatically created by multiple interpolation, and the time-area and time-length curves were drawn using voxel tracking technology. MPR, multiplanar reconstruction.

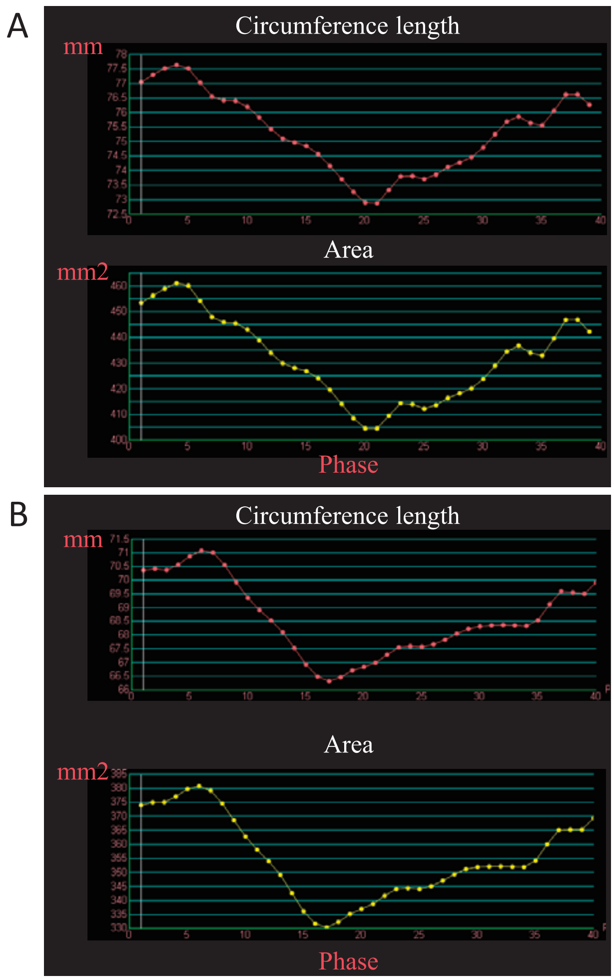


Fig. 2 Variations in the area and circumference of the aortic annulus throughout the cardiac cycle. (A) Control group. (B) Aortic stenosis (AS) group. Note the variations in the aortic circumference length (red lines) and annular area (yellow lines) throughout the cardiac cycle. The horizontal axis of the graph shows the 40 phases during one cardiac cycle.

peak and nadir values of the area and circumference length during one cardiac cycle and identified the shortest phase-to-peak value.

2.4. Data and statistical analysis

Descriptive data are expressed as means ± standard deviation. Normality of data was tested by the Kolmogorov-Smirnov test. Parameters between two groups were compared using the Mann-Whitney *U* test and the paired *t*-test (two-tailed). The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed with statistical software (IBM SPSS Statistics for Windows v20; IBM Inc., Armonk, NY, USA).

3. Results

3.1. Patients' characteristics

Altogether, 75 cases were analyzed after five had been excluded because of poor image quality caused by motion artifact or severe calcification. The distributions of the patients' characteristics are shown in Table 1. The aortic valve area (annular level) and peak pressure gradient, which were used to assess the severity of AS, indicated that all patients had severe disease and so were candidates for TAVI (Table 1).

3.2. Comparisons of the AS and control groups

3.2.1. Minimum and maximum area and circumference length values

We measured the maximum and minimum values for the area and circumference length in the aortic annulus and STJ, which were then subjected to body surface area correction (Table 2). There were no significant differences in the areas of the aortic annulus and STJ, but the circumference length was significantly longer in the AS group than in the control group ($p < 0.001$).

3.2.2. Peak phases of the area and circumference length

Smooth time-area and time-length curves were drawn for the area and circumference length in the aortic annulus. The peak phase during which the area reached its maximum value was significantly later in the AS group than in the control group ($p = 0.005$) (Table 2).

3.2.3. Change in rate of area and circumference length

The minimum/maximum values ratio was accepted as the rate of change (Table 3). Results showed that the rates of change in the aortic annulus area, aortic annulus circumference, STJ area, and STJ circumference were significantly smaller in the AS group than in the control group ($p < 0.001$).

3.3. Comparison of the annulus and STJ

3.3.1. Rates of change in area and circumference length

In the control and AS groups, the rates of change in the area and circumference length were significantly greater in the aortic annulus than in the STJ (Table 4).

4. Discussion

There were three main findings in this study. (1) There was no significant difference in the aortic annulus and STJ areas between the AS and control groups, whereas the circumference length was significantly greater in the AS group than in the control group. (2) The phase with the largest aortic annulus area was significantly slower in the

Table 2 Aortic annulus and STJ parameters in all phases in the control group and in patients with severe AS

	Control group (n = 42)	Patients with severe AS (n = 75)	P-value
Aortic annulus			
Min area index (mm^2/m^2)	253.13 ± 36.56	264.97 ± 46.33	0.195
Min circumference index (mm/m^2)	43.26 ± 3.83	50.59 ± 6.72	< 0.001
Max area index (mm^2/m^2)	289.31 ± 41.51	295.28 ± 45.87	0.539
Max circumference index (mm/m^2)	47.56 ± 4.17	53.23 ± 6.50	< 0.001
Max annulus area phase (%)	7.98 ± 4.41	11.80 ± 7.56	0.005
STJ			
Min area index (mm^2/m^2)	374.77 ± 58.44	375.31 ± 72.73	0.807
Min circumference index (mm/m^2)	53.41 ± 5.37	58.81 ± 7.65	< 0.001
Max area index (mm^2/m^2)	400.76 ± 63.74	394.79 ± 77.37	0.503
Max circumference index (mm/m^2)	55.33 ± 5.40	60.39 ± 7.90	0.001

Values are mean ± SD or n (%)
AS = aortic stenosis, Min = minimum, Max = maximum, STJ = sinotubular junction
In order to eliminate the influence of the difference in physique, the area and circumference were divided by body surface area.

Table 3 Change rate of aortic annulus and STJ in control group and in patients with severe AS

	Control group (n = 42)	Patients with severe AS (n = 75)	P-value
Change rate of annulus area (%)	114.37 ± 4.04	111.86 ± 4.47	0.001
Change rate of annulus circumference (%)	113.39 ± 4.03	111.06 ± 4.57	0.003
Change rate of STJ area (%)	106.96 ± 3.49	105.18 ± 2.82	0.001
Change rate of STJ circumference (%)	107.44 ± 3.65	105.47 ± 3.18	0.001

Values are mean ± SD or n (%)
AS = aortic stenosis, STJ = sinotubular junction

Table 4 Comparison change rate of aortic annulus and STJ

	Annulus	STJ	P-value
Change rate of area in control group (%)	114.37 ± 4.04	106.96 ± 3.49	< 0.001
Change rate of circumference in control group (%)	113.39 ± 4.03	107.44 ± 3.65	< 0.001
Change rate of area in AS group (%)	111.86 ± 4.47	105.18 ± 2.82	< 0.001
Change rate of circumference in AS group (%)	111.06 ± 4.57	105.47 ± 3.18	< 0.001

Values are mean ± SD or n (%)
AS = aortic stenosis, STJ = sinotubular junction

AS group than in the control group. (3) The changes in area and circumference length were greater in the aortic annulus than in the STJ in both the AS and control groups.

4.1. Comparison with previous studies

Although changes in the area of the aortic annulus and Valsalva during a single heartbeat have been studied previously,[6] those studies were two-dimensional evaluations of a 3D structure. The aortic annulus and the STJ could be seen to be changed in 3D views,[11] but changes in shape could not be viewed in two-dimensional evaluations. The voxel tracking technology of PhyZiodynamics is capable of tracking one voxel in four dimensions without being affected by shape distortions.[12, 13] Hence, evaluating the true elasticity and hardness of the aortic annulus and STJ is possible with 4D evaluation.

4.2. Comparison between AS and controls

When measuring the aortic annulus and STJ, we found no difference in area between the AS and control groups, but there was a significant difference in circumference length. Additionally, the rate of change of the STJ and aortic annulus tended to be larger in the control group than in the AS group. These findings indicate that the aortic annulus and the STJ in AS have complex shapes and lack elasticity, possibly due to severe calcification or arteriosclerosis. The fact that the shape is complex means that a device that maintains morphological conformability is needed that could adhere to the aortic wall. When we compared the phases where the aortic annulus area reached its maximum, we found that the AS group was obviously slower than the control group, and reaching the maximum diameter took approximately twice as long. This finding suggests that the measurement phase for device size determination needs to be delayed in the presence of AS.

4.3. Comparison of the annulus and STJ

The AS and control groups showed a higher rate of change in the area and circumference length in the aortic annulus than in the STJ. This finding suggests that the annulus is more flexible than the STJ. Anatomically, the aortic annulus is a part of the LV outflow tract and is affected by wall motion of the LV wall, whereas the STJ is part of the aortic wall at the junction between the ascending aorta and the Valsalva sinus.[14,15] These differences in anatomical structure may also display differences in flexibility, which our study has indeed shown.

Some of the TAVI devices are designed to be placed from the STJ to the aortic annulus. As many of them are self-expanding, compliance for both the aortic annulus and the STJ is desirable.

4.4. Clinical implications of this study

Recently, self-expanding devices have been used for TAVI. They are appropriately placed to fit the shape of the base of the aorta, with the expectation that the number of complications (e.g., vascular injury) will be reduced.[16] Unlike the original balloon-expandable device, however, the stent structure attached to the prosthetic valve is relatively long, extending beyond the STJ.[17–19]

In this study, we showed the difference in extensibility between the STJ and aortic annulus. Developing a device with expandability that is tailored to offer great extensibility is required. We also showed that morphological conformability is important to maintain close contact with the aortic wall to prevent perivalvular leak.

Furthermore, in the presence of AS, the phase during which the area of the aorta and the surrounding diameter are maximum was later than normal. Therefore, we considered it necessary to set the imaging phase at "slow" during CT imaging by prospective gating.

4.5. Limitations of this study

This study had several limitations. First, this was a retrospective observational study at a single Japanese cardiovascular hospital. Also, "normal" control cases were patients who underwent coronary artery CT with full-phase imaging, and this control group was small. Therefore, the control group may not be completely representative of the general population.

Second, there are many elderly people in the AS group; thus, this study may be influenced by age. However, patients with aortic valve stenosis who are candidates for TAVI are limited to the elderly, and therefore need to be considered as a combined effect including being elderly.

5. Conclusions

Dilatability during the cardiac cycle is different for the aortic annulus and the STJ. Additionally, the phase during which the aortic annulus area is maximum in patients with AS is later than normal. This study may contribute to the development of a safety procedure of TAVI strategy.

Disclaimer: Takanori Ikeda is one of the Editors of Toho Journal of Medicine. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

Acknowledgements: This study was supported by the Sakakibara Clinical Research Grant for Promotion of Science. We thank the staff of Ziosoft Inc. for providing technical support and Tatsunori Niwa for technical assistance. We thank the Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Conflicts of interest: Takanori Ikeda received research funds from Daiichi Sankyo Co., Bayer Yakuhin Co., Medtronic Co. and Japan Lifeline Co. He is also paid by Daiichi Sankyo Co., Ono Pharmaceutical Co., Bayer Yakuhin Co., and Bristol-Myers Squibb Co. for company lectures.

Mitsuaki Isobe received research funds from Daiichi Sankyo Co., Ono Pharmaceutical Co., Chugai Pharmaceutical Co., Otsuka Pharmaceutical Co., and TEIJIN PHARMA. He is also paid by Daiichi Sankyo Co., Ono Pharmaceutical Co., and Chugai Pharmaceutical Co. for company lectures.

Other authors declare that there are no conflicts of interest regarding the publication of this paper.

References

1) Leon MB, Smith CR, Mack M, Miller DC, Moses JW, Svensson LG, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med. 2010; 363: 1597-607.
2) Logeais Y, Langanay T, Roussin R, Leguerrier A, Rioux C, Chaperon J, et al. Surgery for aortic stenosis in elderly patients. A study of surgical risk and predictive factors. Circulation. 1994; 90: 2891-8.
3) Sucha D, Tuncay V, Prakken NH, Leiner T, van Ooijen PM, Oudkerk M, et al. Does the aortic annulus undergo conformational change throughout the cardiac cycle? A systematic review. Eur Heart J Cardiovasc Imaging. 2015; 16: 1307-17.
4) Gurvitch R, Wood DA, Tay EL, Leipsic J, Ye J, Lichtenstein SV, et al. Transcatheter aortic valve implantation: durability of clinical and hemodynamic outcomes beyond 3 years in a large patient cohort. Circulation. 2010; 122: 1319-27.
5) Bertaso AG, Wong DT, Liew GY, Cunnington MS, Richardson JD, Thomson VS, et al. Aortic annulus dimension assessment by computed tomography for transcatheter aortic valve implantation: differences between systole and diastole. Int J Cardiovasc Imaging. 2012; 28: 2091-8.
6) Zhu D, Zhao Q. Dynamic normal aortic root diameters: implications for aortic root reconstruction. Ann Thorac Surg. 2011; 91: 485-9.
7) Hamdan A, Guetta V, Konen E, Goitein O, Segev A, Raanani E, et al. Deformation dynamics and mechanical properties of the aortic annulus by 4-dimensional computed tomography: insights into the functional anatomy of the aortic valve complex and implications for transcatheter aortic valve therapy. J Am Coll Cardiol. 2012; 59: 119-27.
8) Kazui T, Izumoto H, Yoshioka K, Kawazoe K. Dynamic morphologic changes in the normal aortic annulus during systole and diastole. J Heart Valve Dis. 2006; 15: 617-21.
9) Achenbach S, Delgado V, Hausleiter J, Schoenhagen P, Min JK, Leipsic JA. SCCT expert consensus document on computed tomography imaging before transcatheter aortic valve implantation (TAVI)/transcatheter aortic valve replacement (TAVR). J Cardiovasc Comput Tomogr. 2012; 6: 366-80.
10) Nagao M, Yamasaki Y, Kamitani T, Kawanami S, Kondo M, Sonoda H, et al. Geometrical characteristics of aortic root and left ventricular dysfunction in aortic stenosis: quantification of 256-slice coronary CT angiography. Heart Vessels. 2017; 32: 558-65.
11) Lansac E, Lim HS, Shomura Y, Lim KH, Rice NT, Goetz W, et al. A four-dimensional study of the aortic root dynamics. Eur J Cardiothorac Surg. 2002; 22: 497-503.
12) Masri A, Schoenhagen P, Svensson L, Kapadia SR, Griffin BP, Tuzcu EM, et al. Dynamic characterization of aortic annulus geometry and morphology with multimodality imaging: predictive value for aortic regurgitation after transcatheter aortic valve replacement. J Thorac Cardiovasc Surg. 2014; 147: 1847-54.
13) Wai B, Thai WE, Brown H, Truong QA. Novel phase-based noise reduction strategy for quantification of left ventricular function and mass assessment by cardiac CT: comparison with cardiac magnetic resonance. Eur J Radiol. 2013; 82: e337-41.
14) Piazza N, de Jaegere P, Schultz C, Becker AE, Serruys PW, Anderson RH. Anatomy of the aortic valvar complex and its implications for transcatheter implantation of the aortic valve. Circ Cardiovasc Interv. 2008; 1: 74-81.
15) Veronesi F, Corsi C, Sugeng L, Mor-Avi V, Caiani EG, Weinert L, et al. A study of functional anatomy of aortic-mitral valve coupling using 3D matrix transesophageal echocardiography. Circ Cardiovasc Imaging. 2009; 2: 24-31.
16) Berry C, Asgar A, Lamarche Y, Marcheix B, Couture P, Basmadjian A, et al. Novel therapeutic aspects of percutaneous aortic valve replacement with the 21F CoreValve Revalving System. Card Angiogr Interv. 2007; 70: 610-6.
17) Grube E, Buellesfeld L, Mueller R, Sauren B, Zickmann B, Nair D, et al. Progress and current status of percutaneous aortic valve replacement: results of three device generations of the CoreValve Revalving system. Circ Cardiovasc Interv. 2008; 1: 167-75.
18) Kammler J, Blessberger H, Fellner F, Kypta A, Lambert T, Engl M, et al. Implantation depth measured by 64-slice computed tomography is associated with permanent pacemaker requirement following transcatheter aortic valve implantation with the Core Valve((R)) system. J Cardiol. 2016; 67: 513-8.
19) Schultz CJ, Weustink A, Piazza N, Otten A, Mollet N, Krestin G, et al. Geometry and degree of apposition of the CoreValve ReValving system with multislice computed tomography after implantation in patients with aortic stenosis. J Am Coll Cardiol. 2009; 54: 911-8.