Etiologies of Hemodynamically Significant Aortic Regurgitation and Coronary Cusp Bending: Evaluation by Transesophageal Echocardiography

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Abstract

Background: While the number of patients with aortic regurgitation (AR) has been increasing in the aging society, its etiologies remain to be fully elucidated. Methods: We studied consecutive 126 patients with chronic moderate or severe AR who underwent TEE. After the study subjects were divided into 2 groups by the age of 65 years, AR etiology was examined in each group. Results: In the older group (n = 85), cusp bending was the most frequent cause of AR (48.2%), and right coronary cusp (RCC) was the most common (90.2%). In the younger group (n=41), bicuspid valve was the most frequent cause (36.5%), and cusp bending was less frequent (16.5%). Multivariate analysis revealed that age was the only factor associated with cusp bending. Conclusion: Cusp bending of RCC was the most frequent etiology of AR in the elderly. Because AR caused by cusp bending has a possibility to be mended by aortic plasty, it is important to detect it by TEE especially in the older patients.

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ABSTRACT

Background: While the number of patients with aortic regurgitation (AR) has been increasing in the aging society, its etiologies remain to be fully elucidated. We examined the causes of AR in the elder patients by analyzing transesophageal echocardiography (TEE) images.

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Methods: We studied consecutive 132 patients with chronic moderate or severe AR who underwent TEE for further evaluation of AR. After the study subjects were divided into 2 groups by the age of 65 years, AR etiology, which was confirmed based on the TEE findings, was investigated in each group.

Results: The total number of patients eligible for this study was 126 (mean age 67 ± 12 years), consisting of the older group (n = 85, mean age 74 ± 5 years) and the younger group (n = 41, mean age 52 ± 11 years). In the older group, cusp bending was the most frequent cause of AR (48.2%), and right coronary cusp (RCC) was the most common region to be affected (90.2%). On the other hand, in the younger group, bicuspid aortic valve was the most common etiology (36.5%), and cusp bending accounted for only 19.5% in this group. Subsequently, all the study subjects were re-classified into 2 groups with or without cusp bending. Between these 2 groups, only age showed a significant difference (p = 0.0017), and multivariate analysis revealed that age was the only factor associated with cusp bending.

Conclusion: Cusp bending of RCC was the most frequent etiology of AR in the elderly. Because AR caused by cusp bending has a possibility to be mended by aortic plasty, it is important to detect it especially in the older patients.

Keywords: valvular heart disease, aortic regurgitation, cusp bending

INTRODUCTION

The prevalence of valvular heart diseases (VHD) is estimated to be 2.5% in developed countries (1). Among VHD, aortic regurgitation (AR) is reported to be the third most common form, following mitral regurgitation (MR) and aortic stenosis (AS) (2). The prevalence of VHD increases especially in patients over 65 years of age because of the predominance of degenerative etiologies (1). Several surveys have been performed to clarify the etiologies of AR so far. Roberts et al. examined 268 patients who had isolated aortic valve (AV) replacement (AVR) for pure AR and concluded that the causes of AR were diverse and the most common category was "cause unclear" in their study (3). In the Euro Heart Survey on VHD, degenerative tricuspid and bicuspid AR were the most common etiologies, accounting for approximately two-thirds of the underlying etiology of AR in the Euro Heart Survey on VHD (4) (5).

In detail, degenerative origin of AR accounted for approximately half (50.3%) and rheumatic AR was present in 15.2%. In addition, Braun et al. reported that RA and other connective tissue diseases can cause valvular disease including AR (6). While AVR has been an established surgical definitive therapy for the treatment of AR, aortic valvuloplasty (AVP) has also been acknowledged gradually as another surgical option for AR (7). Although AVP is not so prevailed as mitral valvuloplasty, both plasty procedures have more advantages such as freedom from anticoagulant therapy. It is essential to conduct precise anatomical assessment preoperatively for a successful valvuloplasty and for the prevention of recurrence of significant regurgitation (8). Recent advancement in echocardiography enables to detect more detailed abnormal morphology of aortic cusps accurately. Cusp bending of aortic valve has been detected more commonly with AR on transesophageal echocardiography (TEE) examination, which is observed as a fibrous band on a cusp (Figure 1, 2, 3, 4) (9) (10) (11). Nevertheless, the prevalence of cusp bending and its clinical characteristics remain to be clarified in pure AR patients. Therefore, the aim of this study was to thoroughly examine the etiologies of AR through observing aortic valve morphology by use of TEE images.

Study Population

We retrospectively studied consecutive 146 patients with chronic moderate or severe AR who underwent TEE for further evaluation of AR in our institution between April 2013 and April 2020. The exclusion criteria were as follows: age of less than 18 years, acute AR, previous history of ascending aortic replacement and/or aortic valve plasty, concomitant moderate or severe AS, evident previous history of infective endocarditis (IE) on any aortic cusp, and poor echo images. We collected the patients' clinical information by reviewing their medical charts.

Transthoracic and Transesophageal Echocardiography

Transthoracic echocardiography (TTE) examinations were performed with a commercially available machine (IE33 or EpiQ CVx, Philips Medical System, USA) ultrasound system equipped with a 2- to 3.5-MHz transducer in the left lateral decubitus position. On top of conventional echo measurements, AR severity was evaluated comprehensively and graded in 3 grades (mild, moderate, severe) in accordance with the guidelines of the American Society of Echocardiography (12) (13). The study subjects of this study were those with moderate or severe AR. In addition, after a consent form of TEE was obtained from every patient, TEE was performed with a transducer (X7-2t or X8-2t) for further evaluation of AR within 3 months after the TTE examination. 2D and 3D TEE grayscale and color images were acquired at the level of the aortic valve and root in all the patients. All images were stored digitally and transferred onto a dedicated image server for subsequent review.

Assessment of AR Etiologies

The recorded echocardiographic images were reviewed off-line for the assessment of AR etiologies by 2 experienced observers who had no medical information about the patients beforehand. Aortic cusp bending was defined as a fibrous band on a cusp on TEE images (Figure 1-1, 2).

Statistical Analysis

As to continuous data, they are expressed as mean values ± standard deviation (SD) if they meet normal distribution. If not, their median and inter-quartile ranges are described. All data were compared by Student's t-test or Wilcoxon rank sum test whenever appropriate. On the other hand, categorical data were presented as percentages and compared by chi-square or Fisher exact test. Univariate and multivariate regression analyses were used to identify clinical variables that were associated with aortic cusp bending. JMP ver12.0 (SAS Institute, Cary, USA) was used for statistical analyses. A p value of < 0.05 was considered statistically significant.

RESULTS

Patients Characteristics

Based on the exclusion criteria, 20 patients were excluded from this study (2 cases of ascending aortic replacement and/or aortic valvuloplasty, 2 cases of moderate or severe AS, 16 cases of IE). In total, 126 patients were eligible for this study (mean age 67 ± 12 years, male 73%). Table 1 shows their baseline clinical characteristics, comorbidities and echocardiographic measurements. Three fourths of the study subjects were hypertensive, and 43% of them had chronic kidney disease (CKD) (estimated glomerular filtration rate < 60 ml/min/1.73m^2). Thirteen (10%) patients had a connective tissue disease (rheumatic arthritis 5, systemic lupus erythematosus 2, Marfan syndrome 1, Takayasu arteritis 1, autosomal dominant polycystic kidney disease 2, polymyalgia rheumatica 1, Behçet's disease 1). More than half of them had severe AR, resulting in their dilated left ventricular (LV) size (LV end-diastolic diameter: 60 mm) with slightly reduced LV ejection fraction (51%) as well as slightly dilated sinus of Valsalva (38 mm) (median values, respectively).

Etiologies of AR (Table 2)

In all the study subjects, the most common etiology of AR was cusp bending (33.0%), followed by aortic root enlargement (22.2%), and bicuspid AV (17.4%). Seven (5.5%) patients had both AV cusp bending and aortic root enlargement. Even normal finding was also noted in 7.9% of the subjects. In AV cusp bending, right coronary cusp (RCC) was the most affected (90.5%, 38 out of 42 cusp bending cases).

Comparison between Cusp Bending and Non-Cusp Bending Groups(Table 3)

As the next step, all the study subjects were classified into 2 groups with or without aortic cusp bending on any cusp. The number of patients with cusp bending was 49 (mean age 72 ± 7 years), whereas that of those without cusp bending was 77 (mean age 64 ± 14 years). The age was significantly higher in the cusp bending group (p = 0.0017). While the patients with aortic cusp bending had significantly lower height (159 vs 165 cm, median, p = 0.0037) and less body surface area (1.58 versus 1.63 m^2, median, p = 0.0287), LV echo measurements did not differ between the 2 groups. However, those with cusp bending had smaller diameters

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of Valsalva sinus (36 vs 39 mm, median, p = 0.0188), ST junction (30 vs 33 mm, median, p = 0.0150) and mid-ascending aorta (35 vs 38 mm, median, p = 0.0097). In addition, patients with mitral prolapse were observed only in the cusp-bending group (8% vs 0%, p = 0.0053).

AR Etiologies According to Age (Table 4)

Subsequently, all the subjects were re-classified into 2 groups based on their age at 65 years: the elderly group (n = 85, mean age 74 ± 5 years) and the younger group (n = 41, mean age 52 ± 11 years). In the elderly group, cusp bending was the most frequent cause of AR (48.2%), and RCC was the most affected cusp (90.2%). On the other hand, in the younger group, bicuspid AV was the most common etiology (36.5%), and cusp bending accounted for only 19.5% in this group.

To examine the contributing factors to aortic cusp bending, logistic regression analysis was performed with age, hypertension, diabetes, CKD and connective tissue diseases included as dependent variables, which revealed that age was the only factor associated with cusp bending (Table 5).

DISCUSSION

We showed that:

In AR patients over 65 years of age, aortic cusp bending was the most frequent AR etiology. On the other hand, in the younger patients, bicuspid AV was the most observed cause of AR.

Aging was the only significant factor to predict coexisting cusp bending of AV.

Cusp bending could occur in any AV cusp, nevertheless, it was detected on RCC by far the most frequently (45 out of 49 cusp-bending related cases). This was consistent with the previous study, reporting that 70% of the isolated cusp bending was seen on RCC (9). Roberts et al. reported that the most frequent cause of AR was "unclear", accounting for 34% (3). The characteristics of the AR patients with "etiology unclear" were higher age with atherosclerotic diseases, in common with the cusp-bending group in this study. Higher age may also contribute to the result that the patients in this group were shorter in height with smaller body surface area. Recent improvement in TEE image quality has helped to detect cusp-bending more clearly, which may have been included in "etiology unclear". Aging is associated with degenerative changes in cusps in various signaling pathways of molecular levels (14). In this study, however, there were no differences between those with and without cusp-bending in terms of the prevalence of atherosclerotic factors such as hypertension, diabetes, lipid disorder, CKD and smoking. Most of the patients in this study had various atherosclerotic diseases originally, and aging is considered the most influential contributor to occurrence of cusp bending above all. Although the number of patients with mitral prolapse was small (4 of 126 patients), they were detected only in cusp bending group, which may be associated with valvular vulnerability in patients with cusp bending.

There are several classifications of AR, and adaptation of the Carpentier classification originally designed for the mitral valve have been described for AR and can be helpful to understand the mechanism of AR, to guide valve repair technique, and to predict recurrence of AR (15). This scheme classifies dysfunction based on the aortic root and leaflet morphology. Cusp bending belongs to type II, cusp prolapse, in this category. As shown in this report, AV cusp bending may have favorable surgical repairability and outcome such as freedom from bleeding events caused by anti-coagulants or IE (9). Therefore, it is important to detect cusp bending preoperatively.

There are some limitations in the present study. This is a single center study and the number of patients enrolled in this study was relatively small. Secondly, 10 cases (7.9%) were classified as echocardiographically normal finding (Table 2). Even without any abnormality on AV cusps, AR can be generated from imbalanced sizes of aortic annulus, Valsalva sinus and ST junction (16) (17), which may be beyond echocardiographic resolution capability. Further investigation will be required for the validation of our study.

CONCLUSIONS

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Cusp bending of RCC was the most frequent etiology of AR in the elderly. Because AR caused by cusp bending has a possibility to be repaired by AVP, it is important to identify the mechanism responsible for AR especially in the older patients.

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Table 1 Baseline Characteristics and Echocardiographic Parameters in All Patients

Clinical Characteristics	
Age, yrs	67±12
Male, n (%)	93 (73.8)
Height, cm	163 [155-168]
Body Weight, kg	58 [49-65]
Body Mass Index, kg/m^2	21 [19-24]
Body Surface Area, m^2	1.61 [1.47-1.75]
Smoking, n (%)	67 (53.1)
Comorbidity	
Hypertension, n (%)	95 (75.3)
Dyslipidemia, n (%)	47 (37.3)
Diabetes, n (%)	17 (13.4)
Previous Ischemic Heart Disease, n (%)	25 (19.8)
Atrial Fibrillation, n (%)	28 (22.2)
Connective Tissue Disease, n (%)	13 (10.3)
Mitral Prolapse, n (%)	4 (3.1)
Steroid User, n (%)	7 (5.5)
Maintenance Dialysis, n (%)	2 (1.5)
Chronic Kidney Disease, n (%)	55 (43.6)
eGFR, ml/min/1.73m^2	57 [42-70]
Echocardiographic Parameters	
LVEDD, mm	60 [53-66]
LVESD, mm	46 [38-53]
LVEF, %	51 [38-59]
IVSD, mm	10 [9-11]
PWD, mm	10 [9-11]
Aortic Root Dimensions	
Annulus Diameter, mm	23 [21-26]
Sinus of Valsalva Diameter, mm	38 [33-43]
ST Junction Diameter, mm	31 [28-38]
Mid-Ascending Aorta Diameter, mm	37 [33-42]
AR Severity	
Moderate, n (%)	29 (23.0)
Moderate to Severe, n (%)	27 (21.4)
Severe, n (%)	70 (55.6)

LVEDD: Left Ventricular End-Diastolic Diameter, LVESD: Left Ventricular End-Systolic Diameter, LVEF: Left Ventricular Ejection Fraction, IVSD: Interventricular Septal Diameter, PWD: Posterior Wall Diameter.

Table 2 AR Etiologies in All Patients

Coronary Cusp Bending, n (%)	42 (33.0)
RCC, n (%)	36 (28.5)
LCC, n (%)	2 (1.5)
NCC, n (%)	2 (1.5)
RCC+NCC, n (%)	2 (1.5)
Aortic Root Enlargement, n (%)	28 (22.2)
Aortic Root Enlargement + RCC Bending, n (%)	7 (5.5)
Bicuspid Aortic Valve, n (%)	22 (17.4)
Coaptation Failure Due to Calcification of Cusps, n (%)	10 (7.9)
Normal Finding, n (%)	10 (7.9)
Chronic Ascending Aortic Dissection, n (%)	2 (1.5)
Quadricuspid Aortic valve, n (%)	1 (0.7)
RCC Flail, n (%)	1 (0.7)
RCC+LCC Prolapse, n (%)	1 (0.7)
RCC Prolapse Due to VSD, n (%)	1 (0.7)
Restrictive RCC with Membranous Interventricular Septal Aneurysm, n (%)	1 (0.7)
Total, n (%)	126 (100)

RCC: Right Coronary Cusp, LCC: Left Coronary Cusp, NCC: Non Coronary Cusp, VSD: Ventricular Septal Defect.

Table 3 Comparison of Baseline Characteristics and Echocardiographic Parameters between "Cusp bending" and "Non Cusp Bending" Patients

	Cusp Bending (n=49, 38.5%)	Non Cusp Bending (n=77, 61.5%)	P value
Clinical Characteristics			
Age, yrs	72±7.1	64±14	0.0017
Male, n (%)	35 (71.4)	58 (75.3)	0.6288
Height, cm	159 [154-164]	165 [156-169]	0.0037
Body Weight, kg	54 [49-62]	59 [50-67]	0.0959
Body Mass Index, kg/m^2	21 [19-24]	21 [19-24]	0.9880
Body Surface Area, m^2	1.58 [1.44-1.64]	1.63 [1.48-1.77]	0.0287
Smoking, n (%)	27 (55.1)	40 (51.9)	0.7293
Comorbidity			
Hypertension, n (%)	40 (81.6)	55 (71.4)	0.1887
Dyslipidemia, n (%)	21 (42.8)	26 (33.7)	0.3049
Diabetes, n (%)	8 (16.3)	9 (11.6)	0.4614
Previous Ischemic Heart Disease, n (%)	9 (18.3)	16 (20.7)	0.7820
Atrial Fibrillation, n (%)	14 (28.5)	14 (18.1)	0.1752
Steroid User, n (%)	3 (6.1)	4 (5.1)	0.8255
Connective Tissue Disease, n (%)	5 (10.2)	8 (10.3)	0.9734
Maintenance Dialysis, n (%)	1 (2.0)	1 (1.2)	0.7442
Mitral Prolapse, n (%)	4 (8.1)	0 (0)	0.0053
Chronic Kidney Disease, n (%)	22 (44.8)	33 (42.8)	0.8219
eGFR, ml/min/1.73m^2	55 [41-63]	58 [42-75]	0.2320
Echocardiographic Parameters			
LVEDD, mm	62 [57-67]	59 [51-64]	0.0919

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	Cusp Bending (n=49, 38.5%)	Non Cusp Bending (n=77, 61.5%)	P value
LVESD, mm	48 [41-55]	44 [36-52]	0.1250
LVEF, %	49 [35-56]	53 [39-60]	0.0702
IVSD, mm	10 [9-12]	10 [9-11]	0.4623
PWD, mm	11 [10-12]	10 [9-11]	0.3924
Aortic Root Dimensions			
Annulus Diameter, mm	23 [20-25]	23 [21-26]	0.1275
Sinus of Valsalva Diameter, mm	36 [33-40]	39 [33-47]	0.0188
ST Junction Diameter, mm	30 [27-34]	33 [29-40]	0.0150
Mid-Ascending Aorta Diameter, mm	35 [32-39]	38 [34-44]	0.0097
AR Severity			
Moderate, n (%)	9 (18.4)	20 (26.0)	
Moderate to Severe, n (%)	11 (22.4)	16 (20.8)	
Severe, n (%)	29 (59.2)	41 (53.2)	

LVEDD: Left Ventricular End-Diastolic Diameter, LVESD: Left Ventricular End-Systolic Diameter, LVEF: Left Ventricular Ejection Fraction, IVSD: Interventricular Septal Diameter, PWD: Posterior Wall Diameter.

Table 4

AR Etiologies in Older Patients ([?]65 years old)

Coronary Cusp Bending, n (%)	37 (43.3)
RCC, n (%)	31 (36.4)
LCC, n (%)	2 (2.3)
NCC, n (%)	2 (2.3)
RCC+NCC, n (%)	2 (2.3)
Aortic Root Enlargement, n (%)	17 (20.0)
Coaptation failure due to calcification of the leaflets	9 (10.5)
Normal Finding, n (%)	8 (9.4)
Bicuspid Aortic Valve, n (%)	7 (8.2)
Aortic Root Enlargement+RCC bending	4 (4.7)
Chronic Ascending Aortic Dissection, n (%)	1 (1.1)
RCC Flail, n (%)	1 (1.1)
Restrictive RCC with Membranous Interventricular Septal Aneurysm, n (%)	1 (1.1)
Total, n (%)	85 (100)

RCC: Right Coronary Cusp, LCC: Left Coronary Cusp, NCC: Non Coronary Cusp.

AR Etiologies in Younger Patients (<65 years old)

Bicuspid Aortic Valve, n (%)	15 (36.5)
Aortic Root Enlargement, n (%)	11 (26.8)
Coronary Cusp Bending (RCC Bending), n (%)	5 (12.1)
Aortic Root Enlargement + RCC Bending, n (%)	3 (7.3)
Normal Finding	2 (4.8)

Bicuspid Aortic Valve, n (%)	15 (36.5)
RCC+LCC prolapse	1 (2.4)
Coaptation failure due to calcification of the leaflets	1 (2.4)
RCC Prolapse Due to VSD, n (%)	1 (2.4)
Quadricuspid Aortic Valve, n (%)	1 (2.4)
Chronic Ascending Aortic Dissection, n (%)	1 (2.4)
Total, n (%)	41 (100)

RCC: Right Coronary Cusp, LCC: Left Coronary Cusp, VSD: Ventricular Septal Defect.

Table 5 Logistic Regression Analysis to Detect Independent Factors Associated with Cusp Bending

Factor	Odds Ratio	95%CI	P value
Age, yrs	1.07	1.03-1.13	0.0014
Hypertension, n (%)	1.28	0.49-3.43	0.6096
Diabetes, n (%)	1.73	0.55-5.45	0.3420
Chronic Kidney Disease, n (%)	0.62	0.27-1.40	0.2546
Connective Tissue Disease, n (%)	0.93	0.24-3.54	0.9131

CI: Confidence Interval.